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G10 G12 G17 G1 G2 G7
G8 P10 P2 P9 R6 R7
S10 S12 S13 S3 S4 S5
T14 T15 T20 T21 T22
T2 T3
H4F D18R D27L D82A
D83B L
(56) Documents cited
GB 1426377
GB 1370548
GB 1318552
GB 1128226
GB 777651
WO 79/00465A
US 4007399A
US 3998550A
US 3769963A
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G1A
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# (54) Non-invasive metabolism measurement

(57) Apparatus for measuring the metabolism of body organs, the local oxygen sufficiency of body organs, areas of pathological change in the metabolism of body organs and local metabolic, oxygen-dependent absorption characteristics of organs, non-invasively *in vivo*, comprises: means 20, 21 for directing radiation towards the body surface at two or more wavelengths in the range 700–1300 nm; means 21, 22 for receiving the radiation on re-emergence from the body surface after interaction with the body tissues, to provide reference and measurement signals; and means 25, 26 for processing the reference and measurement signals to provide a signal representing a characteristic of interest.

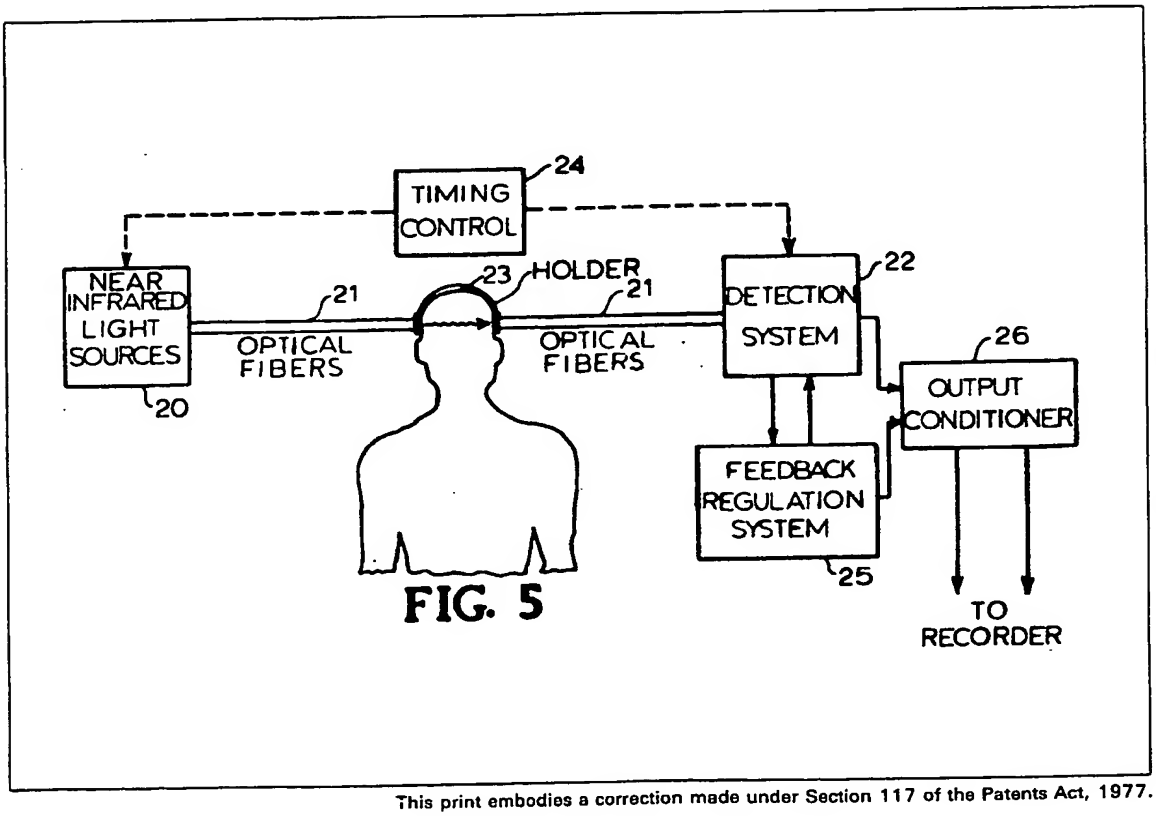



FIG. 5

GB 2 075 668 A

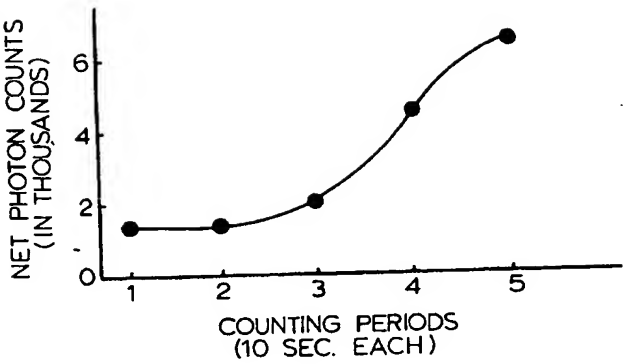

NET PHOTON COUNTS
(IN THOUSANDS)
0
2
4
6
1
2
3
4
5
COUNTING PERIODS
(10 SEC. EACH)

FIG. 1

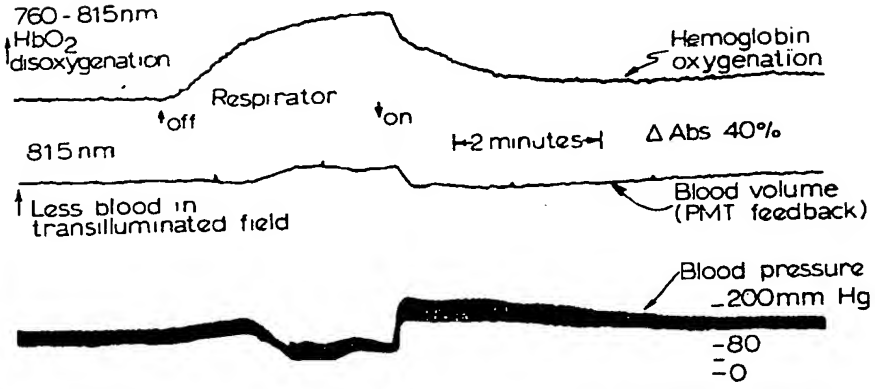
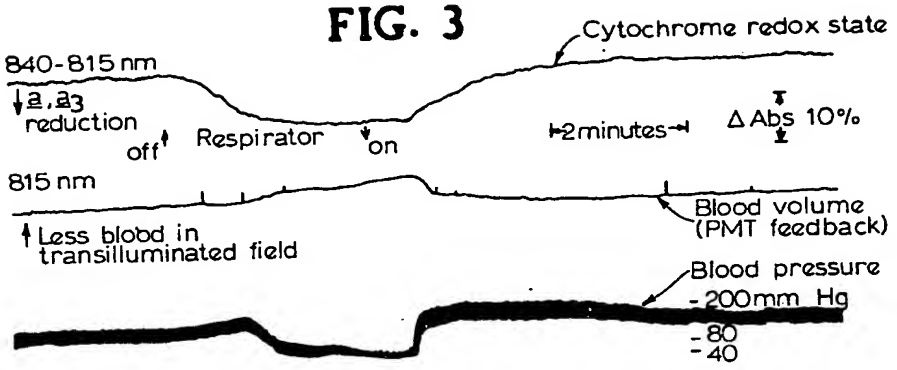

760-815nm
HbO2
disoxygenation
Hemoglobin
oxygenation
Respirator
off
on
2 minutes
Δ Abs 40%
815 nm
Less blood in
transilluminated field
Blood volume
(PMT feedback)
Blood pressure
200mm Hg
80
0

FIG. 2

FIG. 3


Cytochrome redox state
840-815 nm
a, a3
reduction
off
Respirator
on
2minutes
Δ Abs 10%
815 nm
Blood volume
(PMT feedback)
Less blobd in
transilluminated field
Blood pressure
200mm Hg
80
40

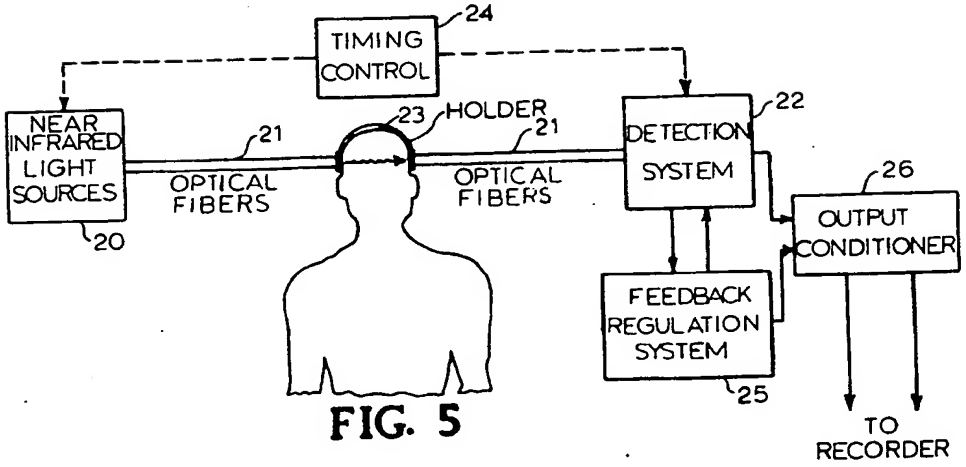

TIMING
CONTROL
24
NEAR
INFRARED
LIGHT
SOURCES
20
21
OPTICAL
FIBERS
23
HOLDER
21
OPTICAL
FIBERS
DETECTION
SYSTEM
22
26
OUTPUT
CONDITIONER
FEEDBACK
REGULATION
SYSTEM
25
TO
RECORDER

FIG. 5

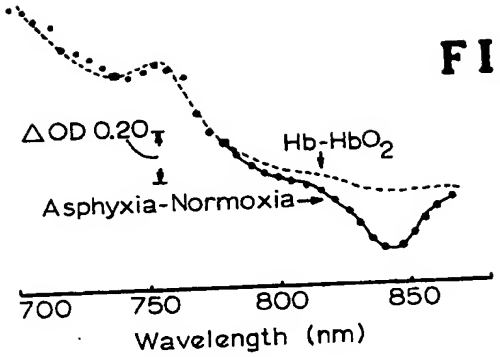



FIG. 4A

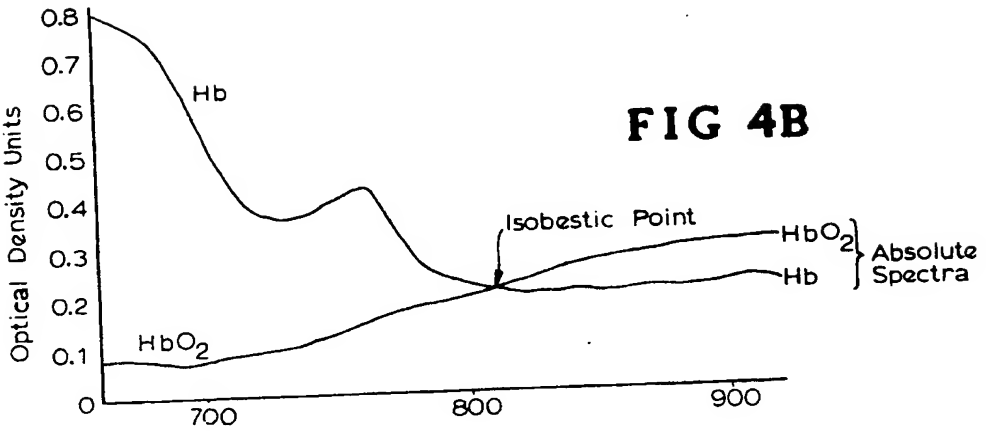



FIG 4B

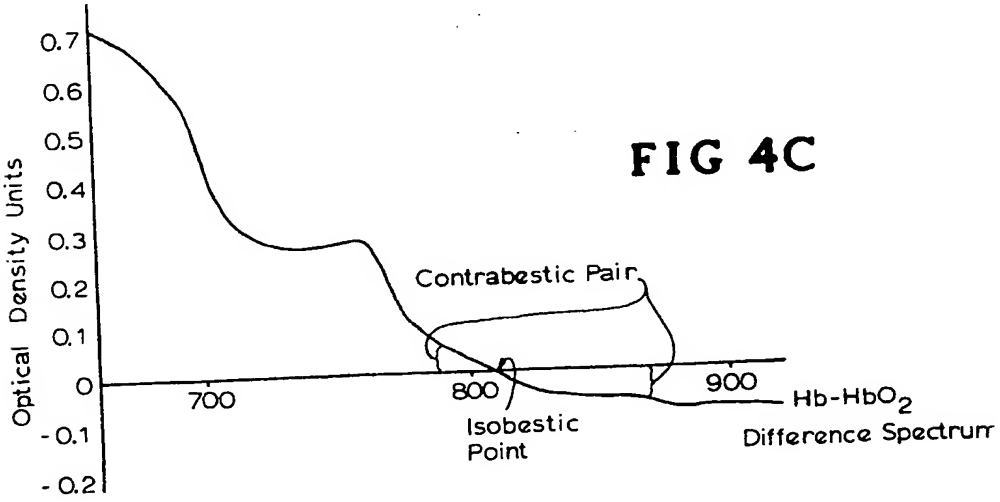



FIG 4C

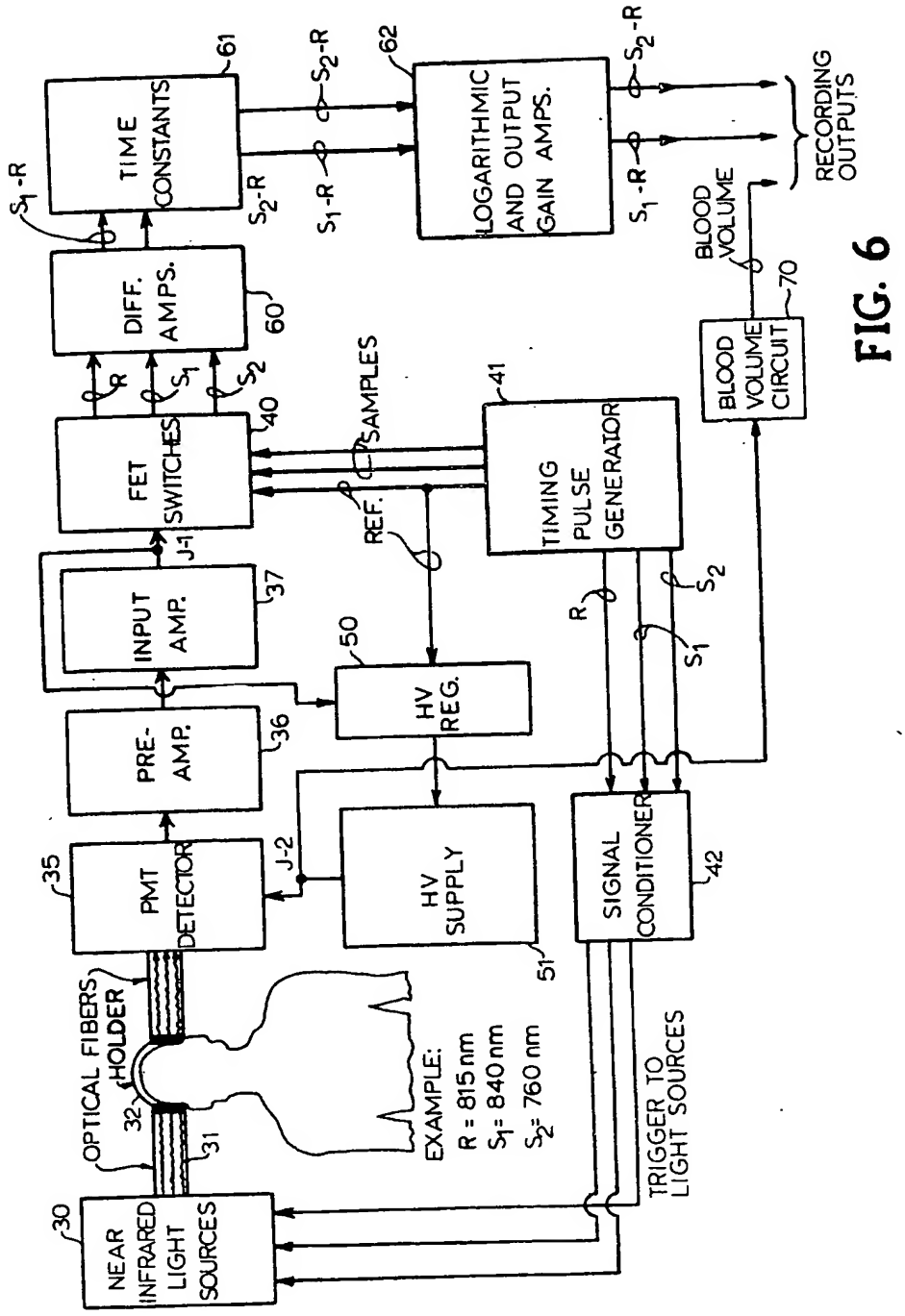

NEAR INFRARED LIGHT SOURCES
30
OPTICAL FIBERS
HOLDER
32
31
PMT DETECTOR
35
J-2
PRE-AMP.
36
INPUT AMP.
37
FET SWITCHES
J-1
40
DIFF. AMPS.
60
TIME CONSTANTS
61
LOGARITHMIC AND OUTPUT GAIN AMPS.
62
RECORDING OUTPUTS
BLOOD VOLUME
BLOOD VOLUME CIRCUIT
70
TIMING PULSE GENERATOR
41
SAMPLES
REF.
HV REG.
50
HV SUPPLY
51
SIGNAL CONDITIONER
42
TRIGGER TO LIGHT SOURCES
EXAMPLE:
R = 815 nm
S1= 840 nm
S2= 760 nm
R
S1
S2
S1-R
S2-R

FIG. 6

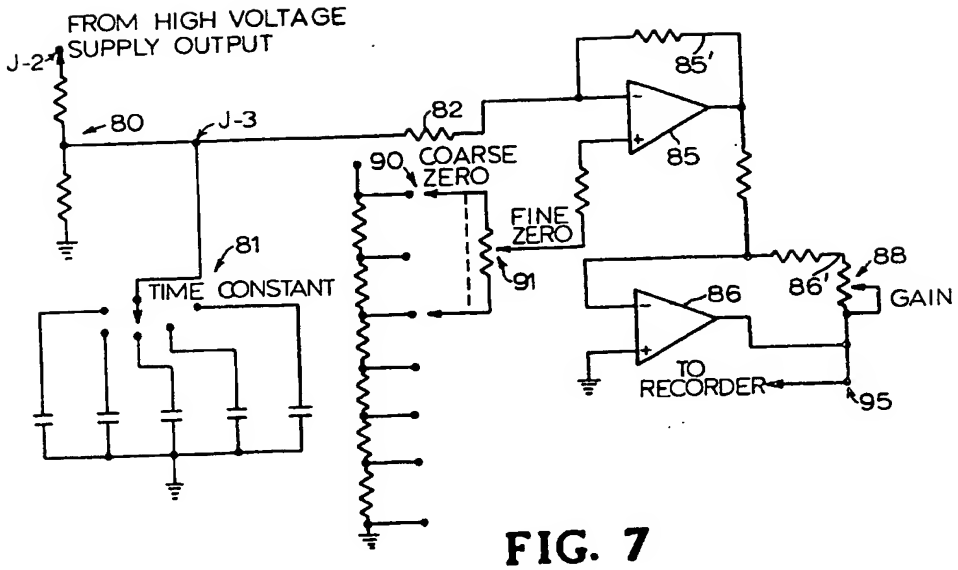



FIG. 7


FIG. 9A

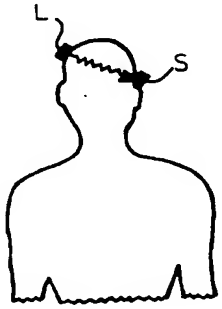



FIG. 9B

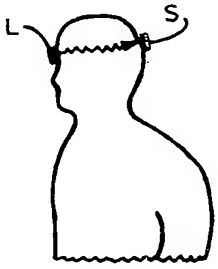



FIG. 9C

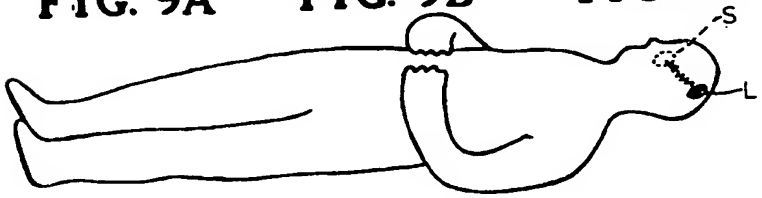



FIG. 9D

2075668

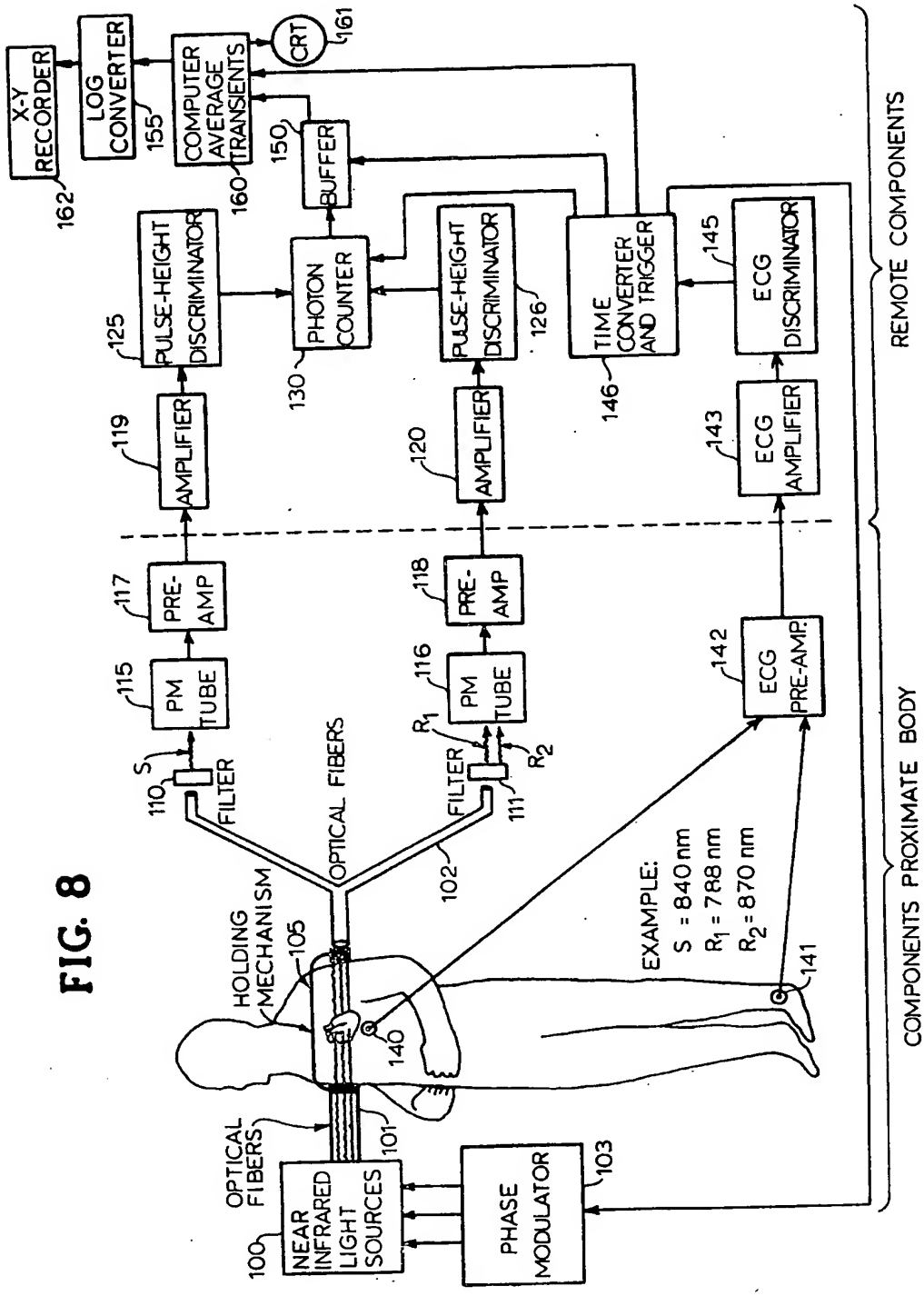



FIG. 8

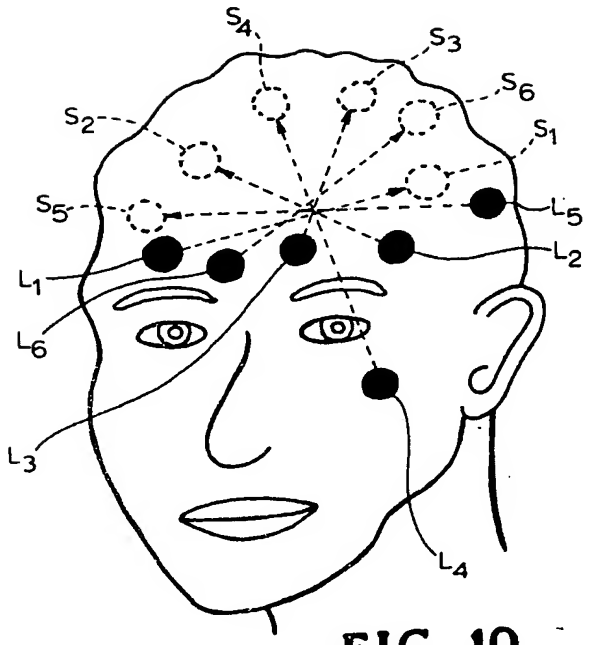

S4
S3
S6
S2
S1
S5
L5
L2
L1
L6
L3
L4

FIG. 10

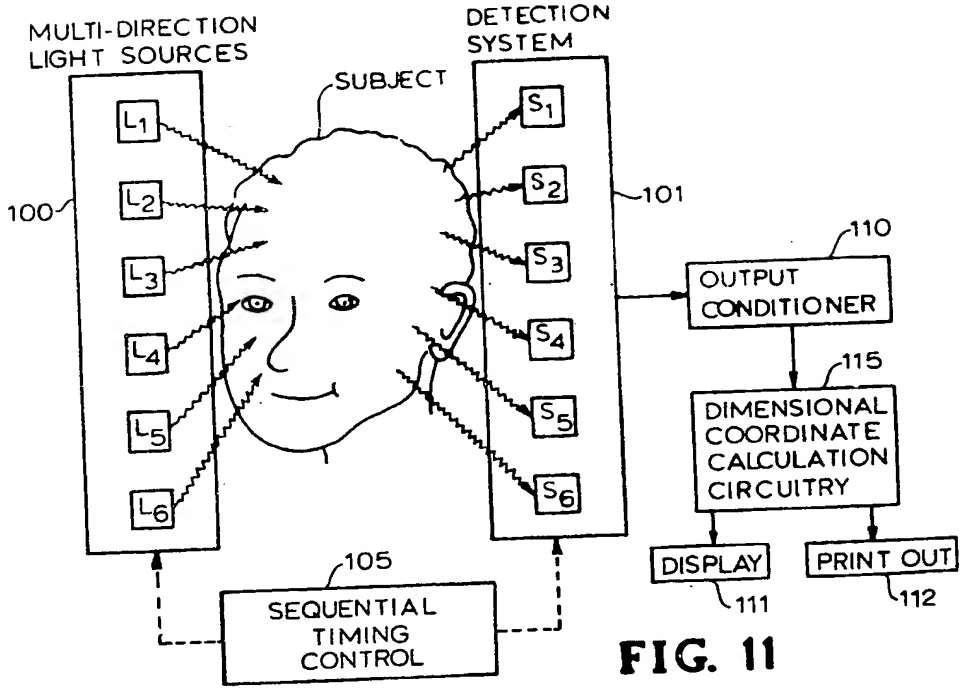

MULTI-DIRECTION LIGHT SOURCES
DETECTION SYSTEM
SUBJECT
100
101
L1
L2
L3
L4
L5
L6
S1
S2
S3
S4
S5
S6
110
OUTPUT CONDITIONER
115
DIMENSIONAL COORDINATE CALCULATION CIRCUITRY
DISPLAY
111
PRINT OUT
112
105
SEQUENTIAL TIMING CONTROL

FIG. 11

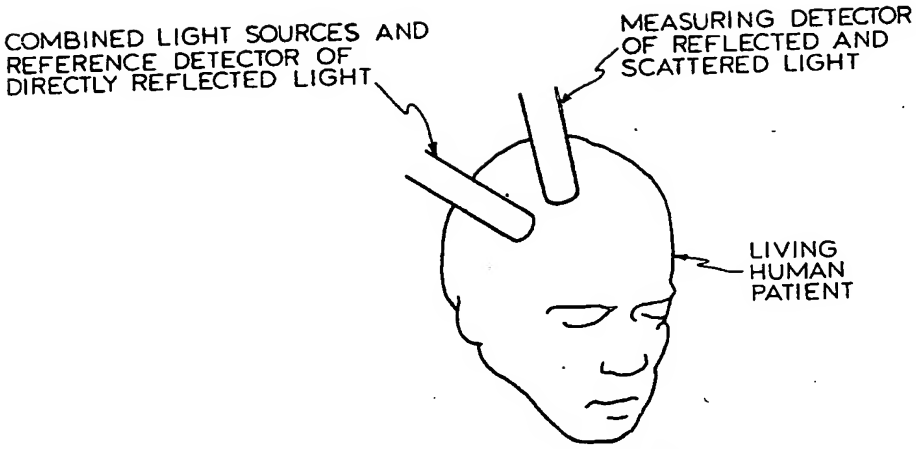

COMBINED LIGHT SOURCES AND REFERENCE DETECTOR OF DIRECTLY REFLECTED LIGHT
MEASURING DETECTOR OF REFLECTED AND SCATTERED LIGHT
LIVING HUMAN PATIENT

FIG. 12

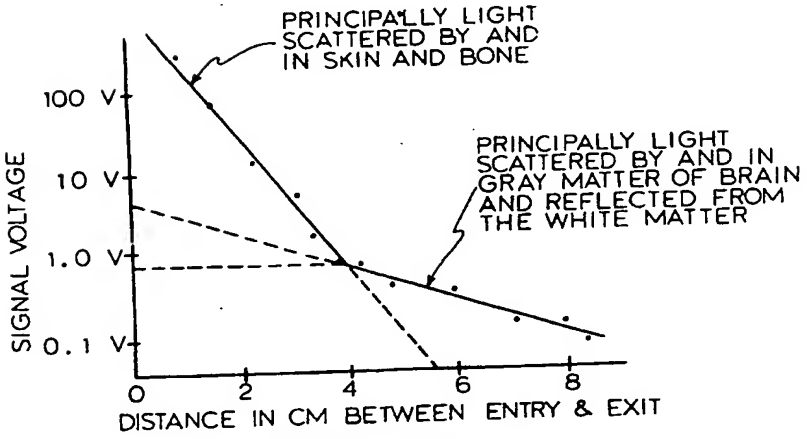

PRINCIPALLY LIGHT SCATTERED BY AND IN SKIN AND BONE
PRINCIPALLY LIGHT SCATTERED BY AND IN GRAY MATTER OF BRAIN AND REFLECTED FROM THE WHITE MATTER
SIGNAL VOLTAGE
100 V
10 V
1.0 V
0.1 V
0
2
4
6
8
DISTANCE IN CM BETWEEN ENTRY & EXIT

FIG. 13

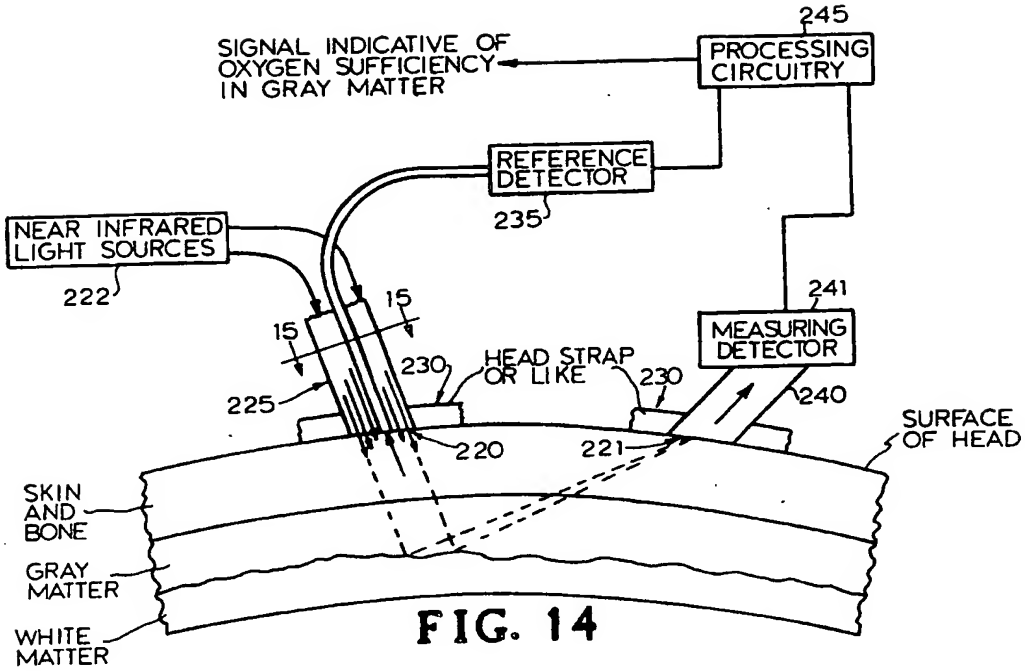



FIG. 14

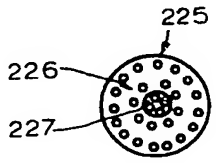



FIG. 15

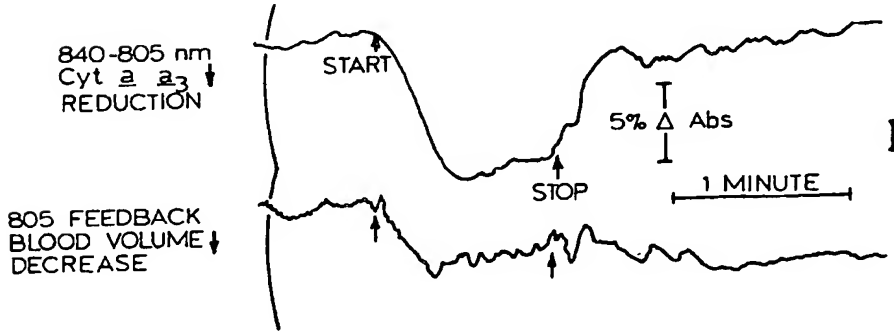



FIG. 16

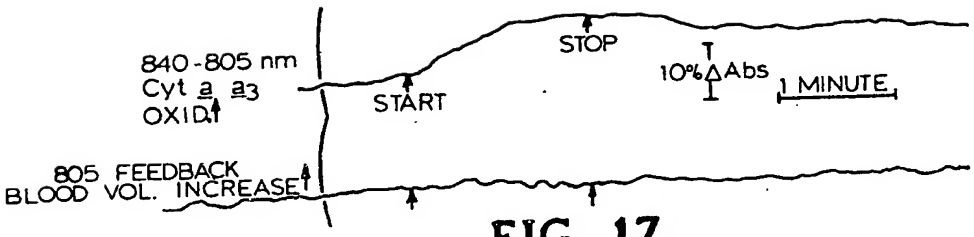



FIG. 17

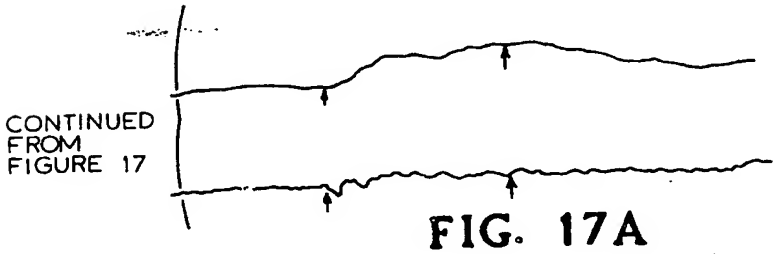



FIG. 17A

SPECIFICATION

**Apparatus for monitoring organ metabolism**

The present invention is concerned with a method for monitoring organ metabolism, for example for monitoring cellular oxidative metabolism by conducting non-invasive, *in vivo, in situ,* measurements of changes in the steady state oxidation-reduction of cellular cytochromes, together with changes in skin and bone, blood volume, organ blood volume, the oxygenation state of haemoglobin and the rate of blood flow in the brain, heart, kidney, other organs, in limbs or other parts of a human or animal body.

It is generally known that metabolism and, more particularly, oxygen sufficiency and adequacy of utilisation are parameters of fundamental importance in assessing the function of any body organ. This is made self-evident when one considers that the energy provision for tissue function is underwritten by more than 94 percent by oxidative reactions involving the reduction of oxygen to water. In the absence of sufficient oxygen, this process becomes impaired, with a corresponding impairment in organ function. In instances of extensive oxygen deprivation, over a period of time the organ loses viability and, as a result, the individual often has the same fate.

Although all organs are adversely affected by oxygen insufficiency, the problem is perhaps the most acute in the case of the brain because of its extreme sensitivity with respect to oxygen demand and its complete dependence on oxidative metabolism for proper function and viability. For example, an absence of oxygen in the brain for more than about 12 seconds produces dysfunction and an absence for more than a few minutes results in irreversible damage. A less acute impairment of oxygen availability leads to a gradual loss of brain function, especially in the higher centres of the cerebral cortex.

Because of the vital role that oxygen sufficency plays in human physiology, intensive efforts have been made over the years to measure this parameter in various organs, particularly in connection with the assessment of brain and heart function. However, a possibility for the direct measurement of this parameter in the intact brain, heart or any other organ by non-invasive means has not previously been available. The prior methods have all been of a secondary nature (e.g., electroencephalographic changes during hypoxia) or indirect and traumatic (e.g. blood flow measurements).

At present, electroencephalograph recordings indicating dysfunction are mainly useful for diagnosis of severely hypoxic or anoxic conditions in the brain. Similarly, electrocardiograph recordings are used to establish an oxygen deficiency in heart muscle. However, such methods are diagnostic only in far-advanced situations and the organ and patient are both in a precarious state before these signals become pathologically indicative.

Measurements of cerebral blood flow and, more recently, of myocardial blood flow are predicated on the assumption that insufficient circulation is the main cause of inadequacy of oxygen delivery to the tissues. Although this assumption is probably correct in the majority of cases, the fact remains that the method is indirect, is beclouded by possibilities of arterial-venous (A–V) shunting and is unable to distinguish inadequate micro-regional blood-flow, especially when accompanied by macro-regional changes.

Local blood flow measurement is presently accomplished by means of radioactive materials introduced into the blood supplying the organ in question during monitoring of local radioactivity of the patient. Administration is either by inhalation of a radioactive isotope of a gas or by arterial or venous injection of a solution containing such a gas. The gas must have sufficient solubility to be easily dissolved in the blood and tissues and its isotope must have a sufficiently strong radiation to penetrate the overlying tissue to be externally monitored. $^{133}$Xenon is commonly employed for this purpose.

The method most commonly used is the wash-out technique after a bolus of a $^{133}$xenon-containing solution has been adminsitered intra-arterially or after breathing a gas mixture containing $^{133}$xenon until a certain degree of saturation of the cerebral tissue has been achieved. $^{133}$Xenon will be rapidly eliminated from blood flowing in the lungs, arterial levels will drop precipituosly and thenceforth the tissue $^{133}$xenon levels will be washed out by equilibration with xenon-free arterial blood. The rate of this process is mainly determined by the rate of blood flow through the observed area. Several compartments with different time courses will usually be observed, the first being the blood itself, others being various fractions of tissue with different circulatory parameters. From these wash-out curves, which take several minutes to be completed, the rate of blood flow in the tissue (or tissues) is then calculated. Deductions about possible circulatory deficiencies are made and translated into further deductions concerning possible deficiencies of oxygen delivery to the tissue. Apart from the indirect nature of the information obtained, serious drawbacks exist in the need to expose the patient to radioactivity.

In yet another procedure, the arterial-venous (A–V) difference technique has been used in efforts to assess the uptake of oxygen across intact organs. This method upon measuring the difference between oxygen concentration in the arterial blood supplying the tissue and the venous blood returning from it.

When used, for example, in brain studies, a sample of arterial blood is drawn from a peripheral artery and a sample of venous blood returning from the head is obtained by means of a hypodermic needle which is inserted into the jugular bulb of the neck. In order also to calculate the rate of oxygen uptake, the total rate of blood flow must be measured. Apart from the fact that the measurement is contaminated with oxygen uptake from structures of the head other than the brain, the method is traumatic and incurs a degree of risk due to the necessity of having to penetrate the jugular bulb. Furthermore, measurements on myocardial oxygen uptake are precluded since pure venous blood from the heart muscle cannot be obtained routinely.

Oximetry techniques have been widely employed for monitoring the arterial blood oxygenation in general. However, such techniques are not directed to providing information primarily concerned with organ or cellular metabolism and more specifically with oxidative metabolism. While oximeter constructions and techniques employed in oximetry are believed to be widely known among those skilled in the art, reference thereto may be found in the book "A Manual of reflection oximetry", W.G. Zijlstra, M.D., 1958, Koninklijke Van Gorcum & Comp. N.V., Assen, Netherlands. A useful background in the literature can be found in the following articles: (1) Review of Scientific Instruments, *13*, 434–444/1942; (2) Principles of Applied Biomedical Instrumentation, L.A. Ceddes & L.E. Baker, pp. 85–91, 1968; (3) Journal of Applied Physiology, *17*, 552–558/1962; (4) Journal of Laboratory and Clinical Medicine, *34*, 387–401/1949; and (5) Annals of Surgery, *130*, 755–773/1949. U.S. Patent Specifications Nos. 3,463,142; 3,647,299; 3,825,342; 3,998,550 and 4,086,915 also describe oximeter techniques.

Transillumination of tissues by a laser beam of visible or near visible light at a low non-hazardous power level not sufficiently intense to cause a reaction of the tissue is discussed in U.S. Patent Specification No. 3,769,963. Fig. 1 of this U.S. Patent Specification also illustrates the use of such a non-hazardous light source as a probe for transillumination over what would appear to be a relatively long optical path possibly including both bone and tissue. U.S. Patent Specifications Nos. 3,764,008 and 4,077,399 also provide useful background information. Transillumination with an intense, incoherent light source as a diagnostic procedure is described on page 373 of the book, "Lasers in Medicine", Leon Goldman, M.D. and R. James Rockwell, Jr., 1971, Gordon and Breach, Science Publishers, Inc., New York, New York. The chapter in this book entitled "Laser Biology" also provides useful background information. Laser transillumination as a diagnostic technique is also discussed on page 130 of the book "Biomedical aspects of the laser", Leon Goldman, M.D., 1967, Springer-Verlag New York Inc. What can be seen from these references is that light passage over relatively long optical paths, including bone, tissue and skin, can be achieved. However, none of these references are directed to the object of the present invention, namely, that of using a relatively non-intense, relatively low power level, coherent light source within the near infra-red region as a non-invasive means for continuously measuring body organ metabolism *in vivo, in situ* and atraumatically.

Circuitry for establishing periodically recurring reference and measuring light pulses and for measuring the detected *in vitro* difference or intensity therebetween is illustrated in U.S. Patent Specifications Nos. 3, 799, 672 and 3,804,535. U.S. Patent Specification No. 3,804,535 also teaches a type of feedback to the photomultiplier voltage supply, as does U.S. Patent Specification No. 3,923,403. Mention of such feedback is made because the circuitry of the present invention utilises a unique type of feedback in an *in vivo, in situ,* non-invasive system to compensate for and monitor the blood volume changes in measurements of organ oxidative metabolism as compared to the reflectance-transillumination systems of the above-mentioned prior art which operate *in vitro* and generally do not produce information related to *in vitro, in situ* oxidative metabolism as does the present invention.

Note should also be made, with reference to U.S. Patent Specification No. 3,804,535, to the fact that use of a reference signal related to an isobestic point, i.e. at which absorbance of oxygenated and deoxygenated (or disoxygenated) blood are equal, has been known as a technique for revealing absorption characteristics of a measuring signal at another wavelength. However, this technique has not previously been employed as a means for compensating for blood volume changes in an *in vivo, in situ* non-invasive system designed to measure cellular and organ oxidative metabolism.

A further aspect of the prior art to be appreciated is the application of the Beer-Lambert Law for determining optical density be determining circuit parameters from the two conditions, namely, of the light being transmitted directly without passing through the test subject, compared with the light being transmitted through the test subject. Various literature sources discuss how this law is applied, one such source being the above-mentioned U.S. Patent Specification No. 3,923,403.

An appreciation of how various combinations of measuring and reference wavelengths have been applied in the prior art for physiological measurements is also deemed useful to

an appreciation of the present invention. In this regard, U.S. Patent Specifications Nos. 3,704,706; 3,709,672; 3,804,535; 3,807,390; 3,811,777; 3,831,030 and 3,910,701 are referred to for background examples of various singular and multiple wavelength combinations, some of which reside within the near infra-red region of interest to the present invention. However, what can be noted with reference to all such prior art is that none of the methods or circuitry apparatus therein disclosed provide means for *in vivo, in situ* monitoring of metabolism and, more specifically, of cellular oxidative metabolism of an internal organ, as in the case of the present invention.

Thus, it is apparent that, while circulatory-respiratory functions, arterial blood oxygenation and blood samples *per se* have been monitored by photometric techniques, presently available apparatus are not suitable for assessing the sufficiency of oxygen and metabolism in general in such vital organs as the brain and heart. Furthermore, such known apparatus do not provide precise information and are often also traumatic. Consequently, an obvious need exists for an apparatus by which this life-sustaining parameter, i.e. cellular oxidative metabolism, can be measured *in vivo* and *in situ* and monitored continuosly with precision and in a non-invasive, non-traumatic manner. Equally important is a need to be able to monitor the blood volume and blood flow rate of the organ being monitored.

It is known that the cellular enzyme cytochrome *a*, $a_3$ (also known as cytochrome *c* oxidase) has a key role in oxidative metabolism, it having been established that the enzyme interacts directly with oxygen and mediates the release of energy during the reduction of oxygen to water. This is achieved by the catalytic donation of four electrons to oxygen and subsequent combination with four H + ions. Under conditions of inadequate oxygen supply, electrons accumulate and the enzyme population shits to a more reduced, steady rate. Consequently, an ability continuously to measure and monitor the redox state of this oxygen-utilising enzyme *in vivo* and *in situ* would provide decisive information on the parameter of oxygen sufficiency in any tissue or organ in question. The present invention provides apparatus with that capability, as well as with the capability of monitoring blood volume and blood flow rate in a manner which is non-invasive and atraumatic.

This is accomplished by optical techniques, the application of which has been made possible by observing that the body and its organs are relatively pervious to low level, non-hazardous light energy in the near infra-red region of the spectrum. Of particular importance, we have found that a beam of relatively low level, non-intense radiation in reference and measuring wavelengths of from about 700–1300 nm can penetrate, be transmitted and be detected and monitored at the end of a relatively long optical transillumination or reflectance path in any selected portion of a human or animal body, which path may include a substantial content of bone, as well as soft tissue and skin.

By fortunate coincidence, cytochrome *a*, $a_3$ has radiation absorption properties in the above-mentioned spectral region, the character of which varies according to its oxidation state. Thus, the present invention is based upon the recognition that it is possible to monitor the redox state of this oxygen-utilising enzyme by means of a spectrophotometric apparatus not previously known.

Thus, the present invention provides an apparatus for measuring the metabolism of the heart in a body *in situ, in vivo,* non-invasively, atraumatically, harmlessly, rapidly and continuously comprising:

(a) a plurality of near infra-red light sources located externally of the body and having light emissions of different wavelength in the 700 to 1300 nanometer spectral range and of an intensity below the level damaging to the body and heart *in vivo* but sufficient to be detectable by a light sensor after transmission along an optical path extending for several centimetres between a pair of points of light source attachment and sensor attachment on the surface of the body and intersecting said heart;

(b) means for sequentially operating said light sources to produce at least one measuring wavelength and at least one reference wavelength within said spectral range for transmission along said path and through said heart and at levels of intensity below that which would be damaging to the body and said heart *in vivo,* each said measuring length being of a value for which the heart *in vivo* exhibits an absorption band for a specific state of metabolic activity, the absorption peak of which changes as the *in vivo* state of activity changes, the measuring wavelength being of a value within the band and closer to the peak than the reference wavelength;

(c) means for monitoring the beat of said heart and triggering the light sources such that said transmitting is accomplished at selected times in rhythm with a selected state of the heart;

(d) attachment means for fixing the output of the light sources to a selected fixed light entry point on the body enabling transmission of the light emissions from the light sources along the path and through the heart such that the absorption thereof becomes dependent upon the *in vivo* state of the metabolic activity of said heart;

(e) means for receiving the transmitted light emissions, including a light sensor fixed to a selected fixed light exit point on the body spaced along the path several centimetres from the entry point and circuit means to

produce for each wavelength a reference signal corresponding to the optical density thereof at the sensor and to produce from the reference signals an electrical output representing the difference in absorption of the heart as a function of each respective set of compared measuring and reference wavelengths and the *in vivo* state of the metabolic activity in the heart; and

(f) means for receiving the electrical output and converting it into a signal providing a substantially continuous and rapid measure of said activity.

The present invention also provides a spectro-photometric apparatus for monitoring the local oxygen sufficiency of a body organ *in vivo, in situ,* non-invasively, atraumatically, harmlessly, rapidly and continuously, comprising:

(a) means for producing near infra-red light at differend wavelengths in the 700 to 1300 nanometer range and of sufficient intensity to be detectable after transmission for several centimetres along an optical path extending through the body and intersecting the organ but with the intensity being below that which would damage the organ *in vivo* or any *in vivo* portion of said body included in the path;

(b) means for selecting at least one measuring wavelength and at least one reference wavelength within the spectral region for transmission through the *in vivo* body organ to be monitored, each measuring wavelength being selected from within one of the absorption bands of oxidised cytochrome *a*, $a_3$ and disoxygenated haemoglobin and each reference wavelength being selected from a spectral region within from about 100 nanometers on either side of a measuring wavelength;

(c) means for locating and fixing the *in vivo* body and said organ with relation to the light means in a position suited for transillumination therethrough along an optical path of several centimetres length extending through the body and intersecting the organ;

(d) means for directing the light at each measuring and reference wavelength and in alternating sequence to one location on the body so as to effect entry therein and passage along a path of several centimetres length through the body intersecting the organ and then to a point of exit from the body;

(e) means for detecting the light emerging from the body at the point of exit therefrom, comparing measuring and reference wavelength intensities and electrically converting the received light to an output signal for each measuring and reference wavelength compared and representing the difference in absorption thereof by the organ *in vivo* as a function of the different wavelengths; and

(f) means for converting each such output signal to a signal substantially continuously and rapidly representative of the changes in the absorption band to which the respective measuring reference wavelengths are related.

Furthermore, the present invention provides an apparatus for determining the localisation of an area of pathological change in the metabolism of a body orgn by measuring local metabolism in selected areas thereof *in situ, in vivo,* non-invasively, atraumatically, harmlessly, rapidly and continuously, comprising:

(a) a near infra-red light source means located externally of the body and having light emissions of different wavelength and of an intensity below the level damaging to the body and the organ *in vivo* but sufficient to be detectable by a light sensor after transmission along an optical path of several centimetres length extending between points of light source entry and exit on the surface of the body and intersecting an area of the organ;

(b) means for operating the light source means to produce, in sequence, at least one measuring wavelength and at least one reference wavelength suitable for transmission along a selected optical path and through a selected area of the organ and at levels of intensity below that which would be damaging to the body and the organ area *in vivo,* each measuring wavelength being of a value for which the organ area *in vivo* exhibits an absorption band for a specific state of metabolic activity, the absorption peak of which changes as the *in vivo* state of activity changes, the measuring wavelength having a value within the band and closer to the peak than the reference wavelength;

(c) light directing means connected to the light source means and enabling the output of the light source means to be directed to a plurality of fixed three dimensionally spaced light entry points on the body in a predetermined sequence for transmission of the light emissions from the light source means for several centimetres along respective optical paths and sequentially through the areas of the organ intersected by the paths and then from the body to respective points of exit such that the absorption thereof becomes dependent upon the respective *in vivo* state of the metabolic activity in the respective areas of the organ;

(d) light receiving means adapted for receiving the transmitted light emissions at the points of exit in a predetermined sequence coordinated with the sequential entry at the entry points, the light receiving means including for each point of exit a light sensor and circuit means to produce for each wavelength and sequentially for each point of exit a signal corresponding to the optical density thereof at the respective exit point sensor and to produce from such signals an electrical output for each exit point in sequence representing the difference in absorption of the organ area illuminated with the respective path as a function of each respective set of compared measuring and reference wavelengths transmitted there-

through and the *in vivo* state of said metabolic activity in the respective area of the organ; and

(e) means for sequentially storing and converting the outputs to a representation of location, size and shape of the area of pathological change.

In addition, the present invention provides a spectrophotometric reflectance apparatus for measuring *in situ, in vivo,* non-invasively, atraumatically, harmlessly, rapidly and continuously a local metabolic, oxygen-dependent activity of a body organ, such activity bearing a measurable relation to an oxygen-dependent absorption characteristic of the organ for a particular wavelength of light transmitted therethrough, comprising:

(a) light source means including:

(i) a plurality of near infra-red light sources located externally of the body and having light emissions of different wavelengths in the 700 to 1300 nanometer spectral range and of an intensity below the level damaging to the body and the organ but sufficient to be detectable by a light sensor after transmission through any skin, bone and tissue included in an optical transmission-reflectance path including the organ and extending for several centimetres between points of light entry and exit laterally spaced several centimetres apart and located on contiguous skin surface areas of the body and after scattering in and reflectance from the organ along the path, the emissions including at least one measuring wavelength and at least one reference wavelength within the spectral range, each measuring wavelength being selected such that the organ exhibits a selective absorption therefor, the extent of which is dependent upon a specific state of a local metabolic, oxygen-dependent activity of the organ;

(ii) means operatively associated with the light sources to produce emissions representing at least one measuring wavelength and at least one reference wavelength within the spectral range for transmission along the path to the organ and at levels of intensity below that which would be damaging to the body and the organ; and

(iii) light transmissions means for receiving, transmitting and directing the output light emissions of the light sources at the measuring and reference wavelengths to a selected fixed light entry point on the body to be transmitted, reflected and scattered along the path and to the organ;

(b) first detector means fixed to the body proximate the entry point for receiving and transmitting the light emissions reflected directly back from the skin, bone and tissue at or within a few millimetres of the point of entry;

(c) second detector means fixed to the body at a fixed light exit point on the body and spaced several centimetres away from the fixed light entry point for receiving and transmitting the light emissions reflected and scattered from the organ;

(d) light sensor and circuit means connected to receive the light emission outputs of the first and second detector means and adapted to produce an electrical output signal corrected for changes in blood volume of the skin, bone and tissue during the measuring cycle and representing the difference in absorption of the measuring and reference wavelengths by the organ as a function of the state of the local metabolic oxygen-dependent activity; and

(e) means for converting the electrical output signal into a signal providing a substantially continuous and rapid measure of the activity.

The spectrophotometric measurements made with the apparatus according to the present invention are made *in vivo* by transmitting near infra-red radiation in at least two different and periodically recurring wavelengths to the test organ *in situ* and detecting and measuring the radiation intensity emerging after transmission through or as reflected from the organ for assessment of biochemical reactions, utilising the previously-mentioned Beer-Lambert Law. One of the wavelengths selected is in a range at which oxidised cytochrome *a*, $a_3$ is highly absorptive. One or two additional wavelengths outside the peak of the cytochrome absorption band but preferably in relatively close proximity to the measuring wavelength are presented in sequence to provide one or more reference signals. A simple subtraction or ratio calculation between the measuring and reference signals is achieved by appropriate circuitry and the non-specific changes in the intensity of transmitted radiation not attributable to absorption by cytochrome *a*, $a_3$ are eliminated.

In one embodiment based on the reflectance technique, the light source and light detector are spaced apart on the same side of the head and the light reflected back to the light source location is detected and used as a correction for skin blood volume changes. Provision is also made for discriminating between light scattered by the grey matter and light reflected from the white matter of the brain and providing a signal known to be indicative of the oxygen sufficiency in the grey matter of the brain. This enables localisation of the area from which signals are obtained.

Although the capability for continuously monitoring cellular oxidative metabolism by monitoring the redox state of cytochrome *a*, $a_3$ in the cells of the selected organ is of principal interest, ancillary data on circulatory parameters related to functioning of the organ can also be obtained in accordance with the transillumination and reflection techniques possible with the apparatus of the present invention. For example, the oxygenation state

of the blood supplied to a given organ can be monitored by the haemoglobin band at slightly different wavelengths, e.g., 740–780 nm, in the above-mentioned near infra-red region of the spectrum. Likewise, data on the total blood volume of the organ can be obtained by monitoring a haemoglobin (Hb)-oxyhaemoglobin ($HbO_2$) isbestic point. This well-known spectrophotometric term refers to a wavelength at which two forms of the same molecule or mixture of molecules have equal absorption intensity. Thus, for oxygenated and disoxygenated haemoglobin, such a point is found to occur between 810 and 820 nm. This variation of stated wavelengths derives from problems arising from the very low optical densities of Hb and $HbO_2$ in this range and the relative insensitivity of most commonly available spectrophotometers in this wavelength range. In practice, any wavelength in the entire range of 815 ± 5 nm can be used without jeopardising the results in situations where the measurements are less sensitive to small errors. A yet wider range of wavelengths can serve the purpose since even small blood volume changes will outweigh the possible interference by Hb ⇄ $HbO_2$ shifts. In another approach, the less practised technique of combining two wavelengths with opposite optical density (OD) responses to the interfering reaction can be combined. Thus, for Hb ⇄ $HbO_2$ equal Δ OD values but of opposite sign occur at 788 and 870 nm. This combination of signals of equal strength but opposite sign at two wavelengths is called a "contrabestic pair". It is especially useful when two reference wavelengths are used straddling the peak to be measured in conditions of intense and changing, wave-length-dependent scattering. A series of wavelengths chosen such that the net sum of their optical density changes becomes zero is another method of cancelling interfering reactions. In contra-distinction thereto, "equibestic" pairs can be used to correct errors arising when the spectral effects of a Hb to $HbO_2$ shift or the reverse predominate. In this case, a reference wavelength is selected which has an equal OD effect in the same direction as the one occurring at the measuring wavelength when the interfering reaction proceeds.

In addition, with either the transillumination or reflectance technique which can be carried out with the apparatus of the present invention, blood flow rates may be monitored, albeit discontinuously, by the rapid administration of a small quantity of a dye, for example cardiogreen, having absorption properties in the near infra-red spectral region or, alternatively, by having the test subject take single breaths of a gas mixture containing a high and low concentration of oxygen in alternating sequence or one breath of a mixture with a small, innocuous admixture of carbon monoxide. By selecting two wavelengths for differentially measuring the optical density of the organ in the spectral region of the absorption band of the dye, an optical signal indicating the arrival and subsequent departure of the dye in the cerebral circulation and dilution in the total blood volume, the so-called transit time, is measured. The latter is directly indicative of the rate of blood flow, as has been proved by Zierler (see "Principles of Applied Biomedical Instrumentation"). Similarly, the optical density differences of the haemoglobin compounds ($HbO_2$, HbCO or other) can be used to provide the optical signal when the inspired air is suddenly and briefly varied.

For a better understanding of the present invention, reference is made to the accompanying drawings, in which:

*Figure 1* is a graphic representation of optical density changes in the human brain at 815 nm *in vivo* plotted against time periods, using the apparatus according to the present invention, during which a progressive cerebral ischaemia occurred as a result of hyperventilating the respiratory system;

*Figure 2* illustrates changes in haemoglobin, blood volume and blood pressure brought about by changes in the radiation absorption characteristics of cerebral haemoglobin in the head of a cat during temporary asphyxia induced by interruption of artificial respiration for three minutes after paralysis of the animal;

*Figure 3* shows the changes in the cytochrome enzyme from an oxidised to a reduced state, the change in blood volume and the change in blood pressure brought about by changes in the radiation absorption properties of cerebral cytochrome *a*, $a_3$ in the course of the same experiment on the cat test subject referred to in the case of Fig. 2;

*Figure 4a* shows a plot of optical density changes at a number of wavelengths performed on a cat by cranial transillumination, the dashed line representing the haemoglobin spectrum and the solid line representing the trend of the data diverging from the haemoglobin difference spectrum;

*Figure 4b* illustrates the absolute absorption spectra of oxygenated haemoglobin ($HbO_2$) and deoxygenated haemoglobin (Hb);

*Figure 4c* shows the spectral differences observed when blood changes from $HbO_2$ to Hb, as is the case in the experiment of normoxia to anoxia illustrated in Fig. 4A, and indicates a contrabestic pair from which blood volume changes, as well as oxygenation changes, may be determined by the apparatus according to the present invention;

*Figure 5* is a generalised block diagram of a system of instrumentation according to the present invention for carrying out monitoring techniques using analogue circuitry;

*Figure 6* is a more detailed block diagram of a system of instrumentation according to the present invention for carrying out monitoring techniques;

*Figure 7* is a detailed circuit diagram of a portion of the feedback circuitry used to provide information of changes in blood volume flow to the organ;

*Figure 8* is a detailed block diagram of a system of instrumentation according to the present invention for carrying out monitoring techniques *in vivo* on a pulsating organ i.e., the heart, *in situ* and for compensating for such pulsations and using counting circuitry;

*Figures 9A, 9B and 9C* illustrate possible positionings of light sources (L) and sensors (S) on the head and Fig. 9D illustrates positioning of the light sources and sensors with the body reclined;

*Figure 10* illustrates the application of the apparatus of the present invention for a tomography-like technique;

*Figure 11* is a schematic diagram of an axial tomography system according to the present invention;

*Figure 12* represents the head of a human patient and illustrates the general use of the apparatus of the present invention as applied in a reflectance technique;

*Figure 13* is a plot of the relation of the distance between light entry and exit locations to the signal voltage and the source of the measured light when using the reflectance technique of Fig. 12;

*Figure 14* diagrammatically illustrates the general use of the apparatus of the present invention as applied using the reflectance technique to the head of a human or animal *in vivo*;

*Figure 15* represents a cross-section taken on line 15–15 of Fig. 14 through a combined light source and reference detector bundle;

*Figure 16* is a representation of the reduction of $Cu_L$ of cytochrome *a*, $a_3$ and decrease of intracranial blood volume during one minute of hyperventilation based on an experiment using the reflectance technique of Fig. 14, the illustrated cytochrome response being deemed fairly typical, while the return of the blood volume trace is more variable but often returns more rapidly to the baseline than illustrated;

*Figure 17* illustrates a further experiment using the reflectance technique of Fig. 14, showing the effect of hypercapnia plus hyperoxia produced by breathing a gas mixture of 5% by volume carbon dioxide and 95% by volume oxygen for 90 seconds; it should here be noted that a long term increase of the base line, as shown, is often recorded after the first episode: the effects of the second and later exposures to the gas mixture tend to be superimposed on this new base line; and

*Figure 17A* represents a continuation of Fig. 17.

A salient feature of the present invention is the observation that light energy in the near infra-red region having wavelengths in the range of from about 700–1300 nm and at a relatively low, non-hazardous density can be made to penetrate both soft tissue and bone surrounding a living organ and in a relatively long optical path and the detected light at the end of the path can be related to oxidative metabolism. This wavelength range has also been proved to be critical since, within the 700 to 1300 nm wavelength range, oxygenated haemoglobin ($HbO_2$) has extremely low absorption chracteristics, whereas disoxygenated haemoglobin (Hb) displays some weak absorption which slowly rises with decreasing wavelengths below 815 nm to a small peak in absorption around 760 nm. Because of these optical properties, the Hb–$HbO_2$ steady state (i.e., the venous-arterial avrage) can be monitored.

In addition and of significant importance, the present invention recognises that cytochrome *a*, $a_3$ in living body tissue also exhibits an oxygen dependent absorption band in the 700 to 1300 nm wavelength range of the spectrum. When this key enzyme in oxidative reactions is in the presence of sufficient oxygen, a weak absorption band exists in the 780 to 870 region, with a maximum at a wavelength of about 820 to 840 nm. The absence of oxygen results in complete reduction of the enzyme and a concomitant disappearance of the absorption band.

Cytochrome *a*, $a_3$ is the terminal member of the mitochondrial respiratory chain and functions as a donor of four electrons to molecular oxygen in the final step of the main pathway of oxidative metabolism in the cells. In this reaction, the electrons are transferred to oxygen from the four metallic redox components of the enzyme, the two iron atoms of the *a* and $a_3$ hemes and two copper atoms. Subsequent or concomitant combination with four hydrogen ions leads to the formation of water. The free energy difference between the hydrogens in the metabolic substrates and in water is partially conserved in the form of high energy phosphate bonds through the oxidative phosphorylation of adenosine diphosphate (ADP) to adenosine triphosphate (ATP). The latter compound serves as the primary free energy carrier in the cell and meets the free energy needs of most of the endergonic reactions required for normal physiological function and cell survival. Since more than 90% of cellular ATP production is by means of oxidative phosphorylation and since oxygen utilisation is governed by the rate of transfer of electrons to oxygen from cytochrome *a*, $a_3$, this enzyme performs a critical role in cellular oxidative metabolism and energetics. In the absence of sufficient oxygen, electrons accumulate in cytochrome *a*, $a_3$ producing a more reduced steady rate. Thus, the present invention recognises that direct measurements on the redox state of this enzyme will provide conclusive data on the adequacy of oxygen availability and its utilisation in living tissues

and organs.

In carrying out a continuous, non-invasive, *in vivo, in situ* monitoring of the redox state of cytochrome *a*, $a_3$, near infra-red radiation of appropriate wavelengths and at a relatively low power level and corresponding relatively low density is presented at one site and is transmitted through or reflected from the organ under investigation and the transmitted or reflected and scattered light emerging at another site is conducted to a photomultiplier tube for detection and measurement.

The monitoring may be conducted in either a dual or triple wavelength mode with one of the wavelengths being selected to provide a measuring signal and the others a reference signal. The measuring wavelength is preferably at about 840 nm, the centre of the cytochrome *a*, $a_3$ absorption peak being observed *in vivo* but the choice is not so limited since other wavelengths in the absorption band can be utilised.

By calculating the difference between the measuring and reference signals, the non-specific changes in transmission or reflectance characteristics not attributable to cytochrome absorption are, in effect, cancelled out. Appropriate electronic circuits are used to amplify and demodulate the separate signals, to convert them to direct current and to subtract them for differential recording.

In one version of the dual mode, the isobestic point of Hb–$HbO_2$ at 815 nm ± 5 nm is used as the reference wavelength, with a feedback control on the signal produced to compensate for changes in blood volume, i.e. a negative feedback circuit connected to the high voltage source which supplies the photomultiplier tube is used to compensate the reference signal for changes in the reference signal level caused by blood volume changes in the tissue being monitored. The voltage adjustment is then maintained in the subsequent interval when the measuring wavelength is transmitted. Since the changes on voltage supplied to the photomultiplier are directly proportional in magnitude to the changes in blood volume over the optical path, in effect, they measure this important circulatory parameter and are recorded.

In the triple wavelength mode, three wavelengths are presented, i.e. the measuring wavelength and two reference wavelengths. The reference wavelengths preferably straddle the measuring wavelength and are in relatively close proximity to it. An appropriate choice would be for one reference wavelength to be about or less than, say, 100 nm lower than the measuring wavelength and the other to be about 100 nm higher. When interference by blood volume changes is present, resort is made to a contrabestic pair for the two reference wavelengths. When Hb ⇄ $HbO_2$ changes predominate over blood volume changes, an equibestic pair is employed.

As has been mentioned above, haemoglobin also possesses oxygen-dependent absorption properties in the near infra-red region of the spectrum, which permits continuous monitoring of the Hb–$HbO_2$ steady state. In practice, advantage is taken of the fact that disoxygenated haemoglobin (Hb) exhibits a relatively weak absorption which slowly rises with decreasing wavelengths below 815 nm to a small peak in the vicinity of about 760 nm. Thus, determinations on the Hb–$HbO_2$ steady state can be made by differential measurements at wavelengths of about 760 nm and 815 nm, with the 815 nm wavelength (Hb-$HbO_2$ isobestic point) serving to provide the reference signal.

It is apparent from the above discussion that the apparatus of the present invention provides a capability using either a transillumination or reflectance technique for *in vivo, in situ*, non-invasive, atraumatic and continuous monitoring of three parameters of crucial significance for organ metabolism and particularly in situations where information on the state of circulatory adequacy and oxygen sufficiency are needed. These parameters include:

1. the adequacy of oxygen availability for normal function of cytochrome *a*, $a_3$, the cellular enzyme which mediates more than 90% of the oxygen consumed in living tissue;
2. the total blood volume in the tissue under question; and
3. the steady-state status of the relative predominance of oxygenated arterial blood ($HbO_2$) and disoxygenated venous blood (Hb).

Additionally, it should be noted that with either the transillumination or reflectance technique, blood flow rate may be monitored as previously set forth and related to the parameters mentioned, while monitoring of the enumerated three parameters may constitute separate methods of monitoring. The apparatus of the present invention can be used for monitoring plural parameters.

All three parameters are preferably continuously monitored in a single system by a triple wavelength technique in which one reference and two measuring wavelengths are alternately presented to the tissue being tested at a rate (>30Hz) providing sufficient time resolution for the monitoring of the most rapid metabolic reactions. An isobestic point of Hb–$HbO_2$ at a wavelength of 815 nm ± 5 nm is used to provide the reference signal which is subtracted from the measuring signal. One of the measuring wavelengths monitors the oxidised cytochrome *a*, $a_3$ peak at about 840 nm, while the other provides a signal on the Hb–$HbO_2$ steady state by monitoring the disoxygenated haemoglobin absorption peak at about 760 nm. The choice of measuring wavelengths is not limited to 760 and 840 nm, since other wavelengths in the cytochrome *a*, $a_3$ and haemoglobin absorption bands are also applicable. However, wavel-

engths of about 760 and 840 nm are generally preferred. The feedback control on the reference signal compensates for blood volume changes and is used to monitor blood volume in the test tissue, i.e., as previously explained, voltage changes in the feedback loop are recorded as a measure of changes in blood volume.

In another example, one wavelength at about 840 nm is used for the measurement of the absorption band of oxidised cytochrome *a*, $a_3$ but the signals obtained from two wavelengths constituting a contrabestic pair in the haemoglobin spectrum are added together to provide correction for and measurement of changes in blood volume in the organ being tested in the same manner as for a single $Hb-HbO_2$ isobestic wavelength. As shown in Fig. 4C, the mathematical difference between absorption changes at the two contrabestic wavelengths is indicative of shifts in the $Hb-HbO_2$ steady state in the organ produced either by changes in the oxygen supply to the organ or by changes or malfunction of its metabolism. Thus, the use of a contrabestic pair of wavelengths straddling the measuring wavelength provides not only a better correction of the cytochrome *a*, $a_3$ signal during the occurrence of blood volume and light scattering changes but simultaneously provides information on shifts in the haemoglobin oxygenation of the blood in the test organ.

The following experiments were carried out, among others using a transillumination technique, to demonstrate the capability of the *in vivo, in situ,* non-invasive, atraumatic method described herein and using the apparatus according to the present invention for achieving a continuous monitoring of oxidative and circulatory parameters in the intact organ of a physiologically functioning test subject. Subsequent description deals with achieving the same capability, using a reflectance technique.

*Experiment I.*

Since the brain is very sensitively dependent upon oxygen for normal function and is readily accessible with minimal interference from overlying tissues, initial experiments were performed on the brain of a cat by transilluminatiion of the intact skull and musculature and skin.

In preparation for the experiment, the animal was anaesthetised with pentobarbital (40 $mg/_{kg}^{1}$), tracheotomised, intubated and provided with femoral arterial and venous cannulae. Hair was removed over an area of approximately 2 sq. cm. at both temples by means of a depilatory agent. The head, which measured 4.86 cm. between temples, was immobilised in a stereotactic holder and a light conducting bundle of optic fibres was applied with firm pressure against the skin at each temple. One bundle transmitted the appropriate wavelengths of near infra-red radiation as a beam of light from two monochromators to one temple, the other conducted the light emerging from the opposite side of the head to a photomultiplier tube for detection and measurement. The optical density at the point of entry at the temple was relatively low and was approximately $2 \cdot 10^{-5}$ watts per square centimetre, which is currently accepted as being a non-hazardous level for human application. Two 6.6 nm spectral bands were presented alternately at a repetition rate of 60 Hertz. Sufficient light was received to be detected and monitored. Electronic circuits, such as previously referred to and further illustrated in Figs. 5, 6 and 7, were employed to amplify and demodulate the separate signals, convert them to direct current and subtract them for a differential read-out. One wavelength band provided the reference signal and the other the measuring signal. For the reference wavelength, the isobestic point of $Hb-HbO_2$ in the 815 nm region was selected. A negative feedback circuit on the high voltage source supplying the photomultiplier compensated the reference signal for blood volume changes in the optical pathway. Since the voltage changes reflect changes in blood volume, they were recorded as an indicator of this parameter. In addition, means were provided for monitoring changes in femoral arterial blood pressure.

Although the above-mentioned circulatory parameters were monitored, the principal purpose of the experiment was to obtain kinetic measurements on cytochrome *a*, $a_3$ and cerebral haemoglobin during a temporary condition of asphyxia induced by interrupting the artificial respiration for a period of three minutes after paralysis of the animal under test. The results obtained, using an analogue detection system, are shown in Figs. 2 and 3 of the accompanying drawings.

Referring to Fig. 2, the top trace shows the signal recorded for the 760–815 nm wavelength difference and indicates the change of haemoglobin from a partially arterial (oxygenated) to a more venous (disoxygenated) condition. The middle trace represents the negative voltage supplying a photomultiplier tube after feedback stabilisation for constant reference signal (815 nm). The rise in the trace indicates a decreasing optical density at this wavelength ($Hb-HbO_2$ isobestic point), which is seen to accompany the fall in blood pressure (lower trace). A measurable decrease in cerebral blood volume apparently occurs when the circulation starts to fall.

The reduction of cytochrome *a*, $a_3$ in the next hypoxic episode during the period of temporary asphyxia is shown in Fig. 3. It is seen that the 840–815 nm difference signal declines in intensity, which indicates movement from the oxidised to the reduced state (top trace). It is also noted that, after artificial

respiration has been resumed, the cellular enzyme is returned to the oxidised state and the absorption properties characteristic of this state reappear. As in Fig. 2, the middle and bottom traces represent, respectively, the occurence of changes in blood volume and blood pressure.

*Experiment II.*

In this experinent, intra-cranial blood volume changes were continuously monitored on a human test subject *in vivo, in situ,* non-invasively and atraumatically. Voluntary hyperventilation, which decreases cerebral circulation by hypocapnia, was used as a functional test on a healthy, adult male having a larger than average head measurement (13.3 cm. diameter at the temples).

In carrying out the experiment, a bundle of light conducting, optical fibres was firmly applied to each temple to provide a coherent light source. One bundle (having an area of 0.567 $cm^2$) transmitted light at a wavelength of 815 nm (the Hb–$HbO_2$ isobestic point) to one temple, while the other conducted the light emerging at the opposite temple to a photon counter for measurement. The optical density at the point of entry at the temple was relatively low and was approximately 48 $\mu$watts per square centimetre. Photon counting rather than the alternative analogue technique was used in order to increase detection sensitivity. Sequential counting periods of ten seconds each were used with one second intervals interspersed between the counts for read-out. Hyperventilation was started shortly before the beginning of the first counting period.

A significant decrease in optical density, reflected in increased net counts (total counts minus background) was observed as the counting periods progressed. This is shown graphically in Fig. 1 of the accompanying drawings. During the course of the experiment, the verbal comments of the test subject were noted, and it was found that they correlated with the recordings on photon counts, i.e., at the begining of the third cunting period, a feeling of dizziness was reported, at the fourth period a more intense dizziness and at the fifth period the subject indicated that he was too dizzy to continue. Thus, the experiment demonstrates a successful, non-invasive, continuous, atraumatic monitoring *in vivo, in situ* of partial cerebral ischaemia in a living human subject.

*Experiment III.*

When tissue becomes anoxic, for example due to a lack of oxygen in the blood supplying it, a comparison of the near infra-red spectrum before and after the event should show a haemoglobin change towards the maximally disoxygenated form and the reduction of cytochrome *a*, $a_3$ should become evident. In Fig. 4A, the results are shown of such an experiment performed on a cat by cranial transillumination. The optical density changes at a number of wavelengths measured between the normally breathing, anaesthetised animal and after death by asphysiation are shown as dots. Using the 740 and 780 nm points for normalisation, the haemoglobin spectrum form *in vitro* measurements was scaled accordingly and is depicted as a broken line. The derivation of these haemoglobin data is illustrated in Figs. 4B and 4C. The solid line in Fig. 4A depicts the trend of the data where they diverge from the haemoglobin difference spectrum. The maximum difference at approximately 840 nm is identified as caused by the reduction of cytochrome *a*, $a_3$. It is seen that, at 815 $\pm$ 5 nm, the contribution of cytochrome *a*, $a_3$ reduction is minimal and can be neglected when this Hb–$HbO_2$ isobestic point is used for feedback against blood volume changes.

*Rate of blood flow.*

As previously noted, the rate of blood flow through a given organ may also be measured by the apparatus of the present invention. The 815 nm feedback signal can be used as a measuring signal or, alternatively, the signal obtained by presenting light of a wavelength in the range where haemoglobin has a more intense absorption, such as between 740–780 nm. One technique used arterial injection of a bolus of dye having absorption in the selected test wavelength. The time taken for the bolus to pass through the optical pathway is then used to calculate the blood flow rate by the so-called transit time technique. In a more preferred variation of the procedure, the test subject inhales a single breath of air containing a small amount of carbon monoxide. The period of time in which the optical signal is affected by the presence in the blood of the first and highest concentration of the haemoglobin-carbon monoxide compound passing through the optical pathway is evident from a decrease in optical density due to the fact that the Hb–CO compound exhibits practically no light absorption properties in the near infra-red range. The temporary decrease in optical density is used to calculate the blood flow rate by recording intensity and time interval, as described in the above-mentioned Zierler reference.

What should be recognised and fully appreciated in the foregoing description is that the success of cerebral IR monitoring of oxygen sufficiency by the apparatus according to the present invention depends upon the rate of oxidative metabolism and, concomitantly, the cytochrome content of extra cerebral tissues being very low in comparison with those of cerebral tissue. Because of the low concentration of cytochrome *a*, $a_3$ in skin and bone tissue and the short optical pathlength com-

pared to the high cerebral cytochrome *a*, $a_3$ concentration and the long optical pathlength through the human brain, the total cytochrome *a*, $a_3$ signal upon transcranial exposure to light is derived predominantly (more than 98%) from brain tissue. The same holds true for the distribution of the total volume of blood. Although the concentration of cytochrome *a*, $a_3$ in heart muscle is much higher, the relative optical path lengths involved in the transillumination and reflectance techniques, using the apparatus of the present invention, through non-myocardial and myocardial tissue of the chest produces a ratio of the same order of magnitude. Thus, a wide range of applications to monitoring of body organ metabolism generally, cellular metabolism and particularly cellular oxidative metabolism are suggested.

In addition to the naturally-occurring compounds discussed so far, i.e. haemoglobin and cytochrome *a*, $a_3$, any other compound absorbing differentially in the near IR, depending upon the metabolic or physiological function of the tissue, can be used for monitoring purpose of such functions. These other compounds may be either as yet unidentified naturally-occurring ones or ones artificially introduced by ingestion or other administration. For one example, the use of indicator dyes having differential optical properties depending upon the local pH is foreseen as a useful further application and extension of the technique since, during oxygen deficiency, the degradation of glucose to lactic acid (glycolysis) occurs and produces considerable shifts in tissue pH.

The apparatus of the present invention can also be used to great advantage in any clinical situation where the oxygen sufficiency of the brain, heart or other organs needs to be continuously monitored and studied. For example, such information is often of critical importance in the course of surgical operations, during treatment of patients in intensive care units and especially in the case of premature babies, as has been previously recognised and discussed in U.S. Patent Specification No. 3,704,706. In the latter situation, the critical question is how much oxygen to give a premature baby. Too much can result in blindness and permanent lung damage, while too little causes brain damage or death. Improvements in monitoring oxygen levels, such as provided by the apparatus of the present invention, can greatly reduce these problems.

Attention will now be turned to further explanation of the circuitry and instrumentation which may be used in the apparatus of the present invention, using either a transillumination technique, for example as in Fig. 5, or a reflectance technique, for example as in Fig. 12.

*Instrumentation*

A portion of the instrumentation of the apparatus of the present invention provides means for measuring the difference in detected optical intensity between periodically recurring reference and measuring light pulses of different wavelength, detected by a photomultiplier tube. Since the prior art, for example U.S. Patent Specification No. 3,804,535, describes such a technique, the following circuit description will primarily be concerned with those aspects of the instrumentation directed to providing the unique array of reference and measuring wavelengths, the feedback circuitry which allows the received reference signal level to be monitored and compensated for blood volume changes in the organ under examination and the associated circuitry which allows the feedback regulated voltage to the detector or the regulating feedback voltage itself to be recorded as a measure of such blood volume change.

A block diagram of the major component systems of instrumentation and apparatus suited for continuous, atraumatic, non-invasive, *in vivo, in situ* infra-red monitoring of internal oxidative metabolism (oxygen sufficiency) and circulatory parameters is illustrated in Fig. 5. The example shown is for transcranial illumination for cerebral monitoring. While illustrated in conjunction with the transillumination technique, much of the instrumentation description will be found directly applicable to employment of the apparatus of the present invention in the later described reflectance technique.

The near infra-red light sources 20 alternately present radiation through optical fibres 21 at different wavelengths, the intensity of which is measured by the detection system 22. A suitable holder 23 is employed to ensure maximum transmission and minimum loss at the points of entry and exit and guard against involuntary displacements. Such a holder may, for example, simply consist of taping the light sources and receivers to the body or may follow an earphone type construction with means to clamp the light sources and receivers in the selected positions.

The timing control 24 controls the rate and sequence of the monochromatic flashes and demodulates the detected light signals. A feedback regulation system 25 allows the detected signal at one wavelength (e.g. a haemoglobin isobestic point) to be kept constant by negative feedback adjustment of the detector sensitivity to compensate for transmission changes brought about by changes in blood volume in the organ being examined during the time of transillumination. The detector sensitivity is then kept constant during the subsequent presentations of the monochromatic flashes at the other wavelengths. In the next cycle, this procedure is repeated. In addition to stabilisation against blood volume

changes, the feedback signal also provides information on these changes. The received reference and measuring signals, as well as the feedback voltage blood volume indicating signal, are all fed through output conditioner circuitry 26 and then to appropriate recording or display means, as hereinafter described. It should again be noted that either the feed back regulated voltage to the detector or the regulating feedback voltage itself may be recorded as a measure of blood volume change.

The infra-red light sources 20 may be either narrow spectral bands (monochromatic light) derived from an incandescent or arc lamp by appropriate filters or monochromators or any of a number of wavelength-specific light sources, such as light emitting diodes (LED's) or diode lasers (LaD's) or other known laser devices. The required power supplies and LED or laser pulse generators will, of course, be understood to be included as part of the light sources 20 and will be suited to relatively low power levels and non-hazardous optical densities, as are appropriate for the present invention. What is important to note here is that the present invention recognises the commercial availability of light sources appropriate for the present invention and, more particularly, that such light sources in the particular reference and measuring wavelengths used according to the present invention can be utilised in relatively long transillumination or reflectance optical paths, *in vivo, in situ* at relatively long non-hazardous optical intensities and non-invasively for monitoring organ and cellular metabolism.

Fig. 6 represents a somewhat more detailed block diagram of the circuitry and instrumentation apparatus of Fig. 5. Fig. 6, like Fig. 5, is selected to represent an analogue circuitry system for transcranial illumination for cerebral monitoring and is intended to provide monitoring information *in vivo, in situ,* non-invasively and continuously related to the state of cellular oxidative metabolism of the brain of the subject being examined. Various combinations of wavelengths, selected according to the present invention, have been previously discussed. The system of Fig. 6 is intended to represent, as an example, the use of two measuring or "sample" wavelengths of 840 nm and 760 nm, respectively, (designated S–1, S–2) and a single reference wavelength of 815 nm (designated R). Note should again be taken here of the critical absorption characteristic of the enzyme cytochrome *a*, $a_3$ with respect to the wavelength 840 nm, the critical haemoglobin oxygenation characteristic exhibited at 760 nm and the fact that 815 nm represents an isobestic point. Thus, the redox state of cytochrome *a*, $a_3$, the state of haemoglobin oxygenation and blood volume are all measurable parameters.

In the embodiment of Fig. 6, it should be noted that further experience with the apparatus of the present invention will indicate combinations of wavelengths other than those shown. It is, therefore, contemplated that instrumentation providing narrow band widths at many centre wavelengths, for example at 10 nm intervals throughout the 740 to 890 nm range, will be used in the apparatus of the present invention to establish other groups of reference and measuring wavelengths appropriate to the apparatus of the present invention.

Continuing the description of Fig. 6, light sources 30 having the three mentioned wavelengths of 760 nm, 815 nm and 840 nm, each preferably confined to a narrow (6 nm) band, transmit through optical fibres 31 and appropriate holder 32 and provide a relatively low, non-hazardous optical intensity at the point of entry. Comparing Fig. 5 and Fig. 6, the detection system 22 shown generally in Fig. 5, is made up in Fig. 6 of a photomultiplier detector 35, a closely coupled preamplifier 36 and input amplifier 37 of conventional construction and connected as indicated in Fig. 6. This system transduces IR light energy into electrical signals.

The timing control 24 of Fig. 5 includes in Fig. 6 the FET switches 40, the timing pulse generator 41 and the signal conditioner 42, the connections of which are as indicated in Fig. 6 and the functioning of which provides means for separating the signals at the different wavelengths and for synchronising the different wavelength presentations and the detection system. Such circuit components as such are well known, both with regard to construction and to function. Equivalent devices may also be used. For example, while FET (Field Effect Transistor) type switches 40 are suggested, any equivalent electronic switching means can be used. The three wavelengths, reference wavelength 815 nm, measuring or sample wavelength 840 nm and measuring or sample wavelength 760 nm, are thus presented, transmitted and detected as periodically recurring light pulses at a relatively low, non-hazardous level and are then separated out for measuring and monitoring purposes.

Continuing the description of Fig. 6, the feedback regulation system 25 of Fig. 4 includes in Fig. 6 a high voltage regulation circuit 50 and a high voltage supply 51 with the associated connections indicated. A more detailed circuit diagram for the blood volume read-out circuit is shown in Fig. 7.

In general, the feedback circuitry fulfills two functions. Such circuitry compensates for changes in optical density produced by changes in the blood volume in the tissue being examined during the monitoring and also provides a recordable signal giving a direct measure of these changes. More specifically, the high voltage regulation of "feedback" circuitry provides a signal for control-

ling the voltage supplying the photomultiplier or other detector, lowering the supply voltage when the reference signal becomes stronger and conversely increasing sensitivity by increasing the voltage when the signal wanes. The level of the reference signal (labelled R) at junction J–1 (Fig. 6) is fed to the high voltage regulation circuit 50 as indicated and such periodic presentation of signal R is controlled by the timing pulse generator 41. Since the reference wavelength is chosen at a haemoglobin isobestic point so as to be sensitive only to blood (haemoglobin) concentration and not to its degree of oxygenation, this mode of operating the apparatus compensates for changes in blood volume in the transilluminated field and additionally provides a useful measurement of blood volume which can be recorded by means of the blood volume circuit 70, shown in more detail in Fig. 7.

To complete the general description of Fig. 6, the output conditioner circuitry 26 of Fig. 5 includes in Fig. 6 the designated differential amplifier circuitry 60, the time constants circuitry 61 and the logarithmic and output gain amplifier circuitry 62. As will be appreciated from the diagrammatic representaion of Fig. 6, the output conditioning circuitry provides the differential signal by subtracting the reference signal (R) from the sample wavelengths $S_1$ and $S_2$ by means of the differential amplifiers 60 and conditions it further by appropriate filtering through time constant circuitry 61 and by further logarithmic and output gain amplifiers 62 to be, respectively, in units of optical density in conformation with the Beer-Lambert Law and compatible to commonly used recording systems, such as strip charts, x–y plotters, oscillographs and the like.

While not fully illustrated in Fig. 6, it will be appreciated from known photometric techniques that either of two methods may be employed for synchronising the different wavelength presentations and the detection system. When lasers, LaD's, LED's or similar easily pulsed sources are employed, the timing pulse generator 41 may be employed to control the pulsers of these devices. Alternatively, when incandescent or arc lamp sources are used, a chopping wheel, controlling presentation of light to different filters or monochromators, may be employed to trigger the timing pulse generator 41 by means of a secondary light source and phototransistor assembly activated by a slot in the chopping wheel. In either case, the timing pulse generator 41 controls the FET switches 40 which demodulate the detector output.

Given the above conceptual description of the present invention, it is readily possible immediately to visualise various forms of feedback circuitry for monitoring the level of the received reference signal R and providing a corresponding blood volume read-out. One such blood volume readout circuitry is illustrated in Fig. 7 and corresponds to the blood circuit 70 indicated in Fig. 6. In Fig. 7, the junction J–2 connects the output of the high voltage supply 51 (Fig. 6) to a voltage divider 80 which, in turn, at junction J–3, is connected to an adjustable time constant circuit 81 and, through resistor 82, to a pair of differential amplifiers 85, 86 having respective feedback loops 85′, 86′, the latter having an adjustable gain 88. Respective coarse zero 90 and fine zero 91 resistor networks provide additional operating adjustments, as indicated in Fig. 7. Output 95 provides the desired signal designed to reflect the changes in blood volume to the organ as these are reflected in changes in the feedback voltage. Mention is again made that either the feedback regulated voltage to the detector or the regulating feedback voltage itself may be recorded as a measure of such blood volume change.

The versatility of the present invention to another application and utilisation of digital, photon counting and differential method circuitry are illustrated in Fig. 8 The instrumentation of Fig. 8 does not show common components, such as power supplies, and the like, and assumes that the problem to be solved is the examination of oxidative metabolic and oxygen sufficiency signals in the beating heart, which produces motion artifacts and may also go through changes in beat intervals, i.e. change frequency. The basic mode of operation is that of providing a stroboscopic operation, timed to the cardiac cycle and utilising a minimum of three wavelengths, one measuring wavelength and two reference ones, straddling the measuring one.

As light sources, laser diodes (LaD's) are preferred because of their narrow bandwidth, small size, sufficiently high but non-hazardous intensity, low voltages, high efficiency and rapid modulation. Alternatively, light emitting diodes (LED's) may be employed with the advantages of LaD's, except for wider bandwidth. Incandescent or arc lamps are less preferred because of lower efficiency, larger size, the need for a means of wavelength selection and a requirement for higher voltages.

As illustrated in Fig. 8, the fibre optics bundle is randomly split into two bundles for the three wavelength system illustrated. While a pair of photomultipliers are shown, the possible configuration of using a single photomultiplier with the housing window pressed directly against the back of the subject is contemplated. In this latter case, the light sources would be used alternately, which is possible at high frequencies of switching so that the heart has not moved significantly between consecutive pulses.

Referring more specifically to Fig. 8, the radiation of three different wavelengths generated by the light sources 100 are transmitted

through three optical fibres 101 into the chest. A large, full, optical fibre bundle 102 receives the transmitted radiation at the other side of the chest and branches into lesser bundles 102′ and 102″. Other fibre optic bundle arrangements could, of course, be employed to effect the light transmission and detection functions being described. An appropriate holding mechanism 105 secures the respective transmitting and receiving optical faces to the subject as shown. Phase modulation circuitry 103 is operated by the time converter and trigger circuitry 146 referred to hereinafter.

Much of the instrumentation of Fig. 8 will be understood from description already set forth. However, recognition should be taken, in interpreting Fig. 8, of the basic distinctions involved in using the apparatus of the present invention for monitoring cellular metabolism *in vivo, in situ,* non-invasively and continuously in the relatively stable size brain, as compared with similar monitoring of cellular metabolism *in vivo, in situ,* non-invasively and continuously of an organ, i.e., the heart, the physical characteristics of which change radically in the course of a heart cycle. Nevertheless, as can be seen from Fig. 8, the apparatus of the present invention is applicable to both types of situations and makes available a form of non-invasive, *in vivo* organ and cellular metabolism monitoring never heretofore available.

Continuing with the description of Fig. 8, the light detector system includes two optical interference filters 110 and 111, one of which is designed to pass only the measuring wavelength and the other of which is designed to pass the two reference wavelengths. Such a system also includes a pair of photomultiplier tubes 115 and 116, preamplifiers 117 and 118, amplifiers 119 and 120, pulse height discriminators 125 and 126 and a differential photon counter 130, all of which components are well known and their respective functions in the illustrated circuitry arrangement of Fig. 8 will be understood. However, the means for timing the photon counter 130 in coordination with the heart cycle and for executing a stroboscopic type operation of the system are believed to be unique to the apparatus of the present invention and are explained hereinafter in more detail.

An electrocardiogram (ECG) is picked up by two standard electrodes 140 and 141 on the arm, leg or chest, whichever is most useful and convenient, and is amplified by an appropriate preamplifier 142, which should be close to the patient, and an amplifier 143, which may be more remote. An appropriate feature of the ECG is selected by the ECG discriminator 145 to provide a trigger for subsequent circuitry through the indicated time converter and trigger circuitry 146. Such selected feature can be any easily and uniquely distinguishable wave property, such as peak height, rate of rise or the like. Subsequently, the "real time to cardiac time converter", forming part of the time converter and trigger circuit 146, measures the time interval between sequential trigger events and digitally divides this period into a standard number of units of, say, 100. Advantage is taken of the observation that, since the mechanical events and, therefore, motion of the heart, are mostly fixed within the cardiac cycle, no matter what the beat frequency, the various mechanical events occur at a constant interval period within the cycle. In other words, they are time locked to the ECG and not to real time.

The cardiac time information is used in one of two ways. If optical information is desired on the entire cardiac cycle, the differential photon counts may be stored in a temporary digital memory, i.e. buffer 150, and read out in the fixed 100 time intervals calculated for that beat by the time converter portion of the time converter and trigger circuit 146. In another mode of operation, the solid state light sources can be activated for short periods only to coincide approximately with the most significant time periods within one beat, programmed in cardiac time of the previous beat. Subsequently, the exact intervals can be selected and read out of the buffer 150, as described before. An important advantage of buffer operation keyed in terms of cardiac time of that particular beat is the ability to reject information derived from cycles aborted by the occurrence of extra-systoles. Recording and display of the information can be accomplished in a variety of ways, such as by a chart recorder, line printer or on paper tape punch. Continuous monitoring as a factor of time can be performed for selected mechanical positions, say, full relaxation and full contraction. In addition, the information on complete cycles can be stored and manipulated as by the computer for average transient 160 in order to improve signal to noise ratio and displayed on the cathode ray tube CRT 161 or passed through log converter 155 and read-out on X–Y plotter 162.

While the illustrated system utilising dual photometers allows substantial flexibility in timing, the present invention contemplates using a single photomultiplier, with the housing window pressed directly against the back. In this application, means are provided for using the light sources alternately, which is possible at high frequencies of switching, so that the heart has not moved significantly.

The fact is also to be understood that the exact placement of the light source and sensor on the body will depend on what organ or portion of the body is of interest at the moment. Thus, as illustrated in Figs. 9A, 9B and 9C, the light source, designated L, and the light receiver, designated S, may be in various positions on the head and with the

head upright or, as in the case of bed-ridden patient or in a patient being examined prone, the orientation of patient, light source and receiver could be as illustrated in Fig. 9D.

Throughout the circuit description, no indication has been made of the various standard components, such as power supplies and the like. Essentially, all of the major components of the illustrated circuitry are known and their individual construction and functions are known. Furthermore, given the broad instrumentation concepts illustrated in Figs. 5–8, it is believed that it is possible immediately to recognise the organisation and functioning of all of the illustrated components and to appreciate other known circuit devices which might be used in the apparatus of the present invention, as herein explained.

*Tomography.*

For localisation of areas of infarct, stroke, oligaemia and ischaemia or other pathological changes in cellular oxidative metabolism, the known techniques of axial tomography are applicable. Fig. 10 schematically illustrates how paired light sources and sensors can be located to establish optical paths in different planes, at different angles and the like, i.e. by using multi-directional transillumination of the organ, calculation of the appropriate wavelength intensity difference in 2 and 3 dimensional co-ordinates will reveal the location, size and shape of the afflicted area. Fig. 11 schematically illustrates the general circuitry arrangement.

Tomographic procedures have been applied in connection with X-ray photography and, more recently, by employing an X-ray scanning technique. In the latter technique, the patient's head is irradiated with coherent beams of X-rays from a source to a detector. Both rotate stepwise around the patient's head and the intensity of radiation is recorded for each set of coordinates. Information on intensity is recorded and analysed for a two dimensional plane by means of a small dedicated computer. A complete scan in one plane requires fifteen to twenty minutes. Additional planes, for extension toward three dimensional localisation and description, need equal exposure times. The limiting difficulty is the strain on the patient in keeping his head immobilised for these extended periods of time.

In practising tomographic techniques using the apparatus of the present invention, light sources 100 in the 700–1300 nm near infrared region and providing a plane of light, such as continuous wave laser diodes, are used for brief, sequential multi-directional transillumination towards a number of detectors located in the detection system 101 on the opposite side of the head, chest or other region of the body, as illustrated by Fig. 10. A sequential timing control 105, such as a ring counter or the like, is used for sequentially energising the light sources L1–L6 in coordination with the sensing. U.S. Patent Specification No. 3,910,701 illustrates one system for sequentially energising six light emitting diodes. An appropriate output conditioner circuit 110 receives the output and passes it to a display 111 or print out 112 through a dimensional cordinate calculation circuitry as illustrated and as indicated by established tomography techniques. By the application of a complete set of detectors around the body part to be transilluminated and a limited number of measuring and reference sources, for example six, as seen in Fig. 10, exposure times can be decreased by at least a factor of ten and probably more. In addition, the information will be obtained non-invasively, *in vivo, in situ* and atraumatically. Such information will directly indicate the areas of oxygen insufficiency or impairment of blood flow or other conditions accompanied by a change in cellular oxidative metabolism, for example tumours. Finally, the near infrared radiation at the power levels and optical densities employed has no cumulative deleterious effects as is the case with X-ray irradiation.

As can be seen from the foregoing description, the spectrophotomeric apparatus of the present invention is broadly adapted to utilise the described discoveries and measuring capabilities of the present invention in either a transillumination or reflectance technique.

The description will now deal with the more distinctive features of the present invention, as applied in a reflectance technique. In this regard, Figs. 12–17A and the related description are directed to application of the apparatus of the present invention, using a reflectance technique for measuring local metabolism in the brain of a living human or animal specimen, i.e. *in vivo*, harmlessly, non-invasively, continuously and rapidly.

As schematically illustrated in Figs. 12, 14 and 15, two spaced-apart locations are chosen, one of which is designated as a point of light entry 220 and the other of which is designated as a point of light exit 221. Advantageously, any bare or bald skin area of sufficient size (1 $cm^2$ approximately) can be used as an entry or exit site, without preparation. As will later be explained with reference to Fig. 13, the spacing between the light entry point 220 and light exit point 221 is critical for purposes of the present invention and particularly so with reference to utilising the apparatus of the present invention in the manner described for measuring local metabolism in the brain of a living human.

An appropriate source of light 222 provides light within the near infra-red region of 700–1300 nm spectral range. Light from light source 222 is transmitted to the light entry location 220 through a fibre optics

the above mentioned LED 230, a display section 303 for displaying whether the number of the memories is incremented or decremented, a display section 304 for displaying that the strobo 301 is ready to emit light, and an outlet port 305 for delivering photographs taken by use of the camera (for example, an instant camera) housed below the harf mirror 300 in the frame 3.

The front panel 4 is further provided with the slot 85 for the photograph holder 73, a cavity 308 wherein a remote control 307 for the camera 305 is housed, an eject key 309 for ejecting the photograph holder 73 from the slot 85, and another eject key 310 for ejecting the remote control 307 from the cavity 308. Over the frame 3 there is disposed a cover 311 for the operational panel 7 carrying the respective keys and knobs 161 to 182, A magazine cover 812 is further provided for exchange of the rotary magazine 15. It is preferable that a colored (e.g., red) transparent filter be located in front of the display sections 302, 303 and 304 and an uncolored transparent filter 315 be in front of the strobe 301.

Figs. 31 to 33 indicate that this embodiment is substantially same as the previous one except for the presence or absence of the camera 305 and a zoom lens 316, with the latter focusing the face imaage B on the photograph 71 at a predetermined magnitude.

A zoom lens 316 permits zooming by rotating a gear 318 formed at a zooming ring 317 by use of a reduced motor (below the lens, though not shown), thus eliminating the need for focus adjustments.

Preferably, the camera 305 is of the instant type or auto-focus type which automatically measures the distance with respect to an object (or the customer) and performs focusing. A built-in motor automatically loads brings a film in place and delivers the film via the outlet 306 after being exposed and developed. An EE (electronic eye) assembly is preferably installed to automatically adjust exposure time.

A shutter in the camera 305 is under control of the remote control 307 leading from a cable (not shown). The length of the cable is such that focusing is possible when the customer is setting on a chair in front of the camera. The amount of light released from the strobe 301 is properly adjusted in advance. These eliminate the need for manual focusing, simplify an exposure mechanism (e,g., for varying exposure time, shutter speed or light amount of the strobe) and permit quick and simple photographing.

The half mirror 300 is secured in a mirror holder 319 which in turn is provided with a rib 322 having an opening 321 for receiving a shaft 320. The rear of the half mirror 300 is overlaid with a cover 325 to screen the interior of the camera 305 except for a front opening 324 in a lens 323 through the half mirror 300 from view. Guide ribs 328 and 329 are respectively disposed on the cover 325 and the front panel 4 to guide the photographs 326 to the delivery port 306 corresponding to a delivery port 327 of the camera 305. In order that incident light via the delivery port 306 does not make visuable the interior 330 via the opening 324, a shutter 331 is fixed to a threaded stud 332 on the front panel 4 in such a way as to close the delivery port 306. The shutter 331 has a rotary shaft 333 and a stop 334 formed therein by bending for preventing the shutter 331 from being depressed below a predetermined level.

With such an arrangement, the photograph 326 is fed from the delivery port 327 of the camera 305 via the guide ribs 328 and 329 and smoothly discharged out of the counterpart 306 of the front panel 4 while being urging down the shutter 331. Further, a wall 335 sorrounding the shutter 331 and the camera accomodations 330 permits only a minimum of introduced light in the neighbourhood of the accomodations 330 in order that the rear of the half mirror 300 is concealed except for an opening area necessary for taking pictures. This results in enhancing the transmission factor of the half mirror 300 and eliminating the need for increasing the light amount of the strobe.

The following will set forth how to operate the camera 305. Mounted on a fixing angle 338 in the camera 305 is a solenoid 337 by means of a threaded stud which is operable in response to actuation of a shutter key 336 on the remote control 306. One end of an actuator 340 is connected to a rod 339 in the solenoid 337 via a threaded stud 341 and a pin 343 is snugly received within a slot 342 in the actuator 340 so that the actuator 340 is slidable with respect to the fixing angle 338. The other end of the actuator 340 is connected to an end of a shutter angle 345 by means of a threaded stud 346 whose other end is operatively connected through a threaded stud 349 to a pressure member 348 of typically plastic which urges a shutter button 347 of the camera 305. A spring 350 is interposed between the actuator 340 and the fixing angle 338 not to urge normally the actuator 340 in the direction of actuating the shutter button 347. By using a pin 352 a pawl 351 is secured rotatable on the actuator 340. A stop 355 is disposed on the actuator 340 to prevent the pawl 351 from rotating against the absorbing force of the solenoid 337 (as depicted by the arrow 353 in Fig. 35). In order that one end of the pawl 351 normally abuts on the stop 355, a spring 356 is interposed between therebetween. There is provided on a predetermined number of ratchets 358 a plurality of pawls 357 which en-

cytochrome *a*, $a_3$. Furthermore, as illustrated in Figs. 17 and 17A, ventilation with a mixture of 95% by volume oxygen and 5% by volume carbon dioxide produces an increased oxidation of cytochrome *a*, $a^3$ but only a small effect on the blood volume. This latter observation is not yet fully understood but it is to be noted that the 5% by volume carbon dioxide by itself produces a more noticeable increase in blood volume. Opposing influences of hyperoxia and hypercapnia are suspected to offset each other.

In summary, there has been disclosed a new approach to monitoring cellular metabolism in a living organ and, more specifically, to monitoring cellular oxidative metabolism *in vivo, in situ,* non-invasively and continuously in a manner not heretofore accomplished and productive of much useful information for the health of the patient. The forms of display available for the information of interest, such as by recorders, oscilloscopes, tapes, printers or the like, will be readily appreciated.

By the terms "organ metabolism", "cellular metabolism", "cellular oxidative metabolism", "metabolic activity" and the like, as used herein, and in the appended claims as being "information" of interest, there is meant the sum of all physical and chemical processes by which energy is made available for use by the organ. Circulatory processes by which the required metabolites are transported to cellular reaction sites are deemed to be included in such terminology, as well as the metabolic reactions within the cells of the organ. The broad concept of examining, with one measuring wavelength, a cellular activity, for example cytochrome *a*, $a_3$ oxygenation, related to a transmission characteristic of such wavelength and the same activity with at least one other reference wavelength of different characteristic and comparing the respective transmitted wavelength intensities as a difference or ratio as a measure of such activity, it is believed will hereafter suggest many as yet unpredictable applications of such concept.

Of particular value in the use of the apparatus of the present invention is that unlike hazardous surgical laser apparatus and the like, the apparatus of the present invention operates well below hazardous light levels known to cause thermal, photochemical or other damaging tissue reactions. The accepted laser safety standard (American National Standard 136.1 – 1976) for the infra-red range allows a Maximum Permissible Exposure (MPE) for skin exposure to a laser beam of 100 milliwatts per square centimetre average power for multiple pulse exposure periods longer than 10 seconds. As a comparison, the presently performed experiments have not employed more than 2.8 milliwatts per square centimetre time average power, i.e., approximately 35 times less than the MPE. Successful experiments have been performed with substantially less intensities.

Finally, it is to be noted that the illustrated tomographic technique in itself suggests many new applications for localisation of information, since the need for such information is so widespread. While the illustrations show plural sets of light sources, it is to be understood that a single set of measuring and wavelengths could be employed and sequentially physically directed to various optical paths or the organ of interest could be scanned by moving the light sources and detectors relative to the body in the manner of the X-ray scanning mentioned above.

CLAIMS

1. Apparatus for measuring the metabolism of the heart in a body *in situ, in vivo,* non-invasively, atraumatically, harmlessly, rapidly and continuously, comprising:

(a) a plurality of near infra-red light sources located externally of the body and having light emissions of different wavelength in the 700 to 1300 nanometer spectral range and of an intensity below the level damaging to the body and heart *in vivo* but sufficient to be detectable by a light sensor after transmission along an optical path extending for several centimetres between a pair of points of light source attachment and sensor attachment on the surface of the body and intersecting said heart;

(b) means for sequentially operating said light sources to produce at least one measuring wavelength and at least one reference wavelength within said spectral range for transmission along said path and through said heart and at levels of intensity below that which would be damaging to the body and said heart *in vivo,* each said measuring length being of a value for which the heart *in vivo* exhibits an absorption band for a specific state of metabolic activity, the absorption peak of which changes as the *in vivo* state of activity changes, the measuring wavelength being of a value within the band and closer to the peak than the reference wavelength;

(c) means for monitoring the beat of said heart and triggering the light sources such that said transmitting is accomplished at selected times in rhythm with a selected state of the heart;

(d) attachment means for fixing the output of the light sources to a selected fixed light entry point on the body enabling transmission of the light emissions from the light sources along the path and through the heart such that the absorption thereof becomes dependent upon the *in vivo* state of the metabolic activity of said heart;

(e) means for receiving the transmitted light emissions, including a light sensor fixed to a selected fixed light exit point on the body spaced along the path several centimetres from the entry point and circuit means to produce for each wavelength a reference sig-

nal corresponding to the optical density thereof at the sensor and to produce from the reference signals an electrical output representing the difference in absorption of the heart as a function of each respective set of compared measuring and reference wavelengths and the *in vivo* state of the metabolic activity in the heart; and

(f) means for receiving the electrical output and converting it into a signal providing a substantially continuous and rapid measure of said activity.

2. A spectrophotometric apparatus for monitoring the local oxygen sufficiency of a body organ *in vivo, in situ,* non-invasively, atraumatically, harmlessly, rapidly and continuously, comprising:

(a) means for producing near infra-red light at different wavelengths in the 700 to 1300 nanometer range and of sufficient intensity to be detectable after transmission for several centimetres along an optical path extending through the body and intersecting the organ but with the intensity being below that which would damage the organ *in vivo* or any *in vivo* portion of said body included in the path;

(b) means for selecting at least one measuring wavelength and at least one reference wavelength within the spectral region for transmission through the *in vivo* body organ to be monitored, each measuring wavelength being selected from within one of the absorption bands of oxidised cytochrome *a*, $a_3$ and disoxygenated haemoglobin and each reference wavelength being selected from a spectral region within from about 100 nanometers on either side of a measuring wavelength;

(c) means for locating and fixing the *in vivo* body and said organ with relation to the light means in a position suited for transillumination therethrough along an optical path of several centimetres length extending through the body and intersecting the organ;

(d) means for directing the light at each measuring and reference wavelength and in alternating sequence to one location on the body so as to effect entry therein and passage along a path of several centimetres length through the body intersecting the organ and then to a point of exit from the body;

(e) means for detecting the light emerging from the body at the point of exit therefrom, comparing measuring and reference wavelength intensities and electrically converting the received light to an output signal for each measuring and reference wavelength compared and representing the difference in absorption thereof by the organ *in vivo* as a function of the different wavelengths; and

(f) means for converting each such output signal to a signal substantially continuously and rapidly representative of the changes in the absorption band to which the respective measuring-reference wavelengths are related.

3. The apparatus according to claim 2, wherein the $Hb-HbO_2$ isobestic point at 815 ± 5 nanometers comprises a reference wavelength.

4. The apparatus according to claim 3, wherein one measuring wavelength comprises 840 ± 5 nanometers and one reference wavelength comprises 815 ± 5 nanometers, said apparatus being adapted to monitor the redox state of the cellular enzyme cytochrome *a*, $a_3$.

5. The apparatus according to claim 3, wherein one measuring wavelength comprises 760 ± 20 nanometers and one reference wavelength comprises 815 ± 5 nanometers, said apparatus being adapted to monitor the oxygenation state of haemoglobin.

6. Apparatus for determining the localisation of an area of pathological change in the metabolism of a body organ by measuring local metabolism in selected areas thereof *in situ, in vivo,* non-invasively, atraumatically, harmlessly, rapidly and continuously, comprising:

(a) a near infra-red light source means located externally of the body and having light emissions of different wavelength and of an intensity below the level damaging to the body and the organ *in vivo* but sufficient to be detectable by a light sensor after transmission along an optical path of several centimetres length extending between points of light source entry and exit on the surface of the body and intersecting an area of the organ;

(b) means for operating the light source means to produce, in sequence, at least one measuring wavelength and at least one reference wavelength suitable for transmission along a selected optical path and through a selected area of the organ and at levels of intensity below that which would be damaging to the body and the organ area in vivo, each measuring wavelength being of a value for which the organ area *in vivo* exhibits an absorption band for a specific state of metabolic activity, the absorption peak of which changes as the *in vivo* state of activity changes, the measuring wavelength having a value within the band and closer to the peak than the reference wavelength;

(c) light directing means connected to the light source means and enabling the output of the light source means to be directed to a plurality of fixed three dimensionally spaced light entry points on the body in a predetermined sequence for transmission of the light emissions from the light source means for several centimetres along respective optical paths and sequentially through the areas of the organ intersected by the paths and then from the body to respective points of exit such that the absorption thereof becomes dependent upon the respective *in vivo* state of the metabolic activity in the respective areas of the organ;

(d) light receiving means adapted for receiving

the transmitted light emissions at the points of exit in a predetermined sequence coordinated with the sequential entry at the entry points, the light receiving means including for each point of exit a light sensor and circuit means to produce for each wavelength and sequentially for each point of exit a signal corresponding to the optical density thereof at the respective exit point sensor and to produce from such signals an electrical output for each exit point in sequence representing the difference in absorption of the organ area illuminated with the respective path as a function of each respective set of compared measuring and reference wavelengths transmitted therethrough and the *in vivo* state of said metabolic activity in the respective area of the organ; and

(e) means for sequentially storing and converting the outputs to a representation of location, size and shape of the area of pathological change.

7. The apparatus according to claim 6, wherein the light emissions are all in the 700 to 1300 nanometer spectral range.

8. The apparatus according to claims 6 and 7, wherein the light source means comprise plural light sources, each productive of the measuring and reference wavelengths and including means to fix one of the light sources to the body at each point of entry and wherein the light receiving means includes plural light sensors and includes means to fix a sensor to the body at each point of exit.

9. A spectrophotometric reflectance apparatus for measuring *in situ, in vivo,* non-invasively, atraumatically, harmlessly, rapidly and continuously a local metabolic, oxygen-dependent activity of a body organ, such activity being a measurable relation to an oxygen-dependent absorption characteristic of the organ for a particular wavelength of light transmitted therethrough, comprising:

(a) light source means including:

(i) a plurality of near infra-red light sources located externally of the body and having light emissions of different wavelengths in the 700 to 1300 nanometer spectral range and of an intensity below the level damaging to the body and the organ but sufficient to be detectable by a light sensor after transmission through any skin, bone and tissue included in an optical transmission-reflectance path including the organ and extending for several centimetres between points of light entry and exit laterally spaced several centimetres apart and located on contiguous skin surface areas of the body and after scattering in and reflectance from the organ along the path, the emissions including at least one measuring wavelength and at least one reference wavelength within the spectral range, each measuring wavelength being selected such that the organ exhibits a selective absorption therefor, the extent of which is dependent upon a specific state of a local metabolic, oxygen-dependent activity of the organ;

(ii) means operatively associated with the light sources to produce emissions representing at least one reference wavelength within the spectral range for transmission along the path to the organ and at levels of intensity below that which would be damaging to the body and the organ; and

(iii) light transmission means for receiving, transmitting and directing the output light emissions of the light sources at the measuring and reference wavelengths to a selected fixed light entry point on the body to be transmitted, reflected and scattered along the path and to the organ;

(b) first detector means fixed to the body proximate the entry point for receiving and transmitting the light emissions reflected directly back from the skin, bone and tissue at or within a few millimetres of the point of entry;

(c) second detector means fixed to the body at a fixed light exit point on the body and spaced several centimetres away from the fixed light entry point for receiving and transmitting the light emissions reflected and scattered from the organ;

(d) light sensor and circuit means connected to receive the light emission outputs of the first and second detector means and adapted to produce an electrical output signal corrected for changes in blood volume of the skin, bone and tissue during the measuring cycle and representing the difference in absorption of the measuring and reference wavelengths by the organ as a function of the state of the local metabolic oxygen-dependent activity; and

(e) means for converting the electrical output signal into a signal providing a substantially continuous and rapid measure of the activity.

10. The apparatus according to claim 9, wherein the means operatively associated with the light sources comprises means for sequentially operating the light sources.

11. The apparatus according to claim 9 or 10, wherein the light transmission and the first detector means are structurally combined and removably secured to the body at the point of entry.

12. The apparatus according to any of claims 9 to 11, wherein the light sensor and circuit means include means for utilising the light emissions reflected back from the skin, bone and tissue at the point of entry to correct for variations in output of the light sources during said measuring operation.

13. The apparatus according to any of claims 9 to 12, wherein, when intended for carrying out measurements on the brain, the points of light entry and exit comprise spaced points on the head and wherein the light sensor and circuit means include means adapted for sensing and electrically processing

the light emissions reflected back at the point of entry in a manner enabling reflected and scattered light received at the exit point mainly from the skin, bone and tissue of the head to be discriminated from reflected and scattered light received at a more distant exit point from the grey and white matter of the brain, whereby, in said processing, the signal is developed as indicative of oxygen sufficiency in the grey matter.

14. The apparatus according to any of claims 9 to 13, wherein the light sources and the means for sequentially operating the light sources produce at least two reference wavelengths comprising a contrabestic pair and the light sensor and circuit means are adapted for processing the sum of the absorption changes at the two contrabestic wavelengths to produce a signal indicative of blood volume changes and being further adapted for using the difference of the absorption changes in the wavelengths to produce a signal indicative of changes in oxygenation of the blood in the organ.

15. The apparatus according to any of claims 9 to 14, wherein the activity is one of cellular metabolism and the wavelengths operate in reference thereto.

16. The apparatus according to any of claims 9 to 14, wherein the activity is one of cellular oxidative metabolism and the wavelengths operate in reference thereto.

17. The apparatus according to any of claims 9 to 14, wherein the activity is that of the redox state of the enzyme cytochrome *a*, $a_3$ and the wavelengths operate in reference thereto.

18. The apparatus according to any of claims 9 to 14, wherein the activity is that of haemoglobin oxygenation in the organ and the wavelengths operate in reference thereto.

19. The apparatus according to any of claims 9 to 14, wherein the activity is that of local changes in blood volume in the organ, including means for establishing a feedback voltage to maintain, at a predetermined level, the reference signal corresponding to a selected reference wavelength and monitoring the voltage as a measure of the volume.

20. The apparatus according to any of claims 9 to 14, wherein the measured activity is that of the redox state of the enzyme cytochrome *a*, $a_3$ in the organ.

21. The apparatus according to any of claims 9 to 20, wherein the light sources and means for operating the light sources are adapted to produce a pair of reference wavelengths comprising a contrabestic pair.

22. Apparatus according to any of the preceding claims for monitoring metabolism in body organs, substantially as hereinbefore described and with reference to the accompanying drawings.

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